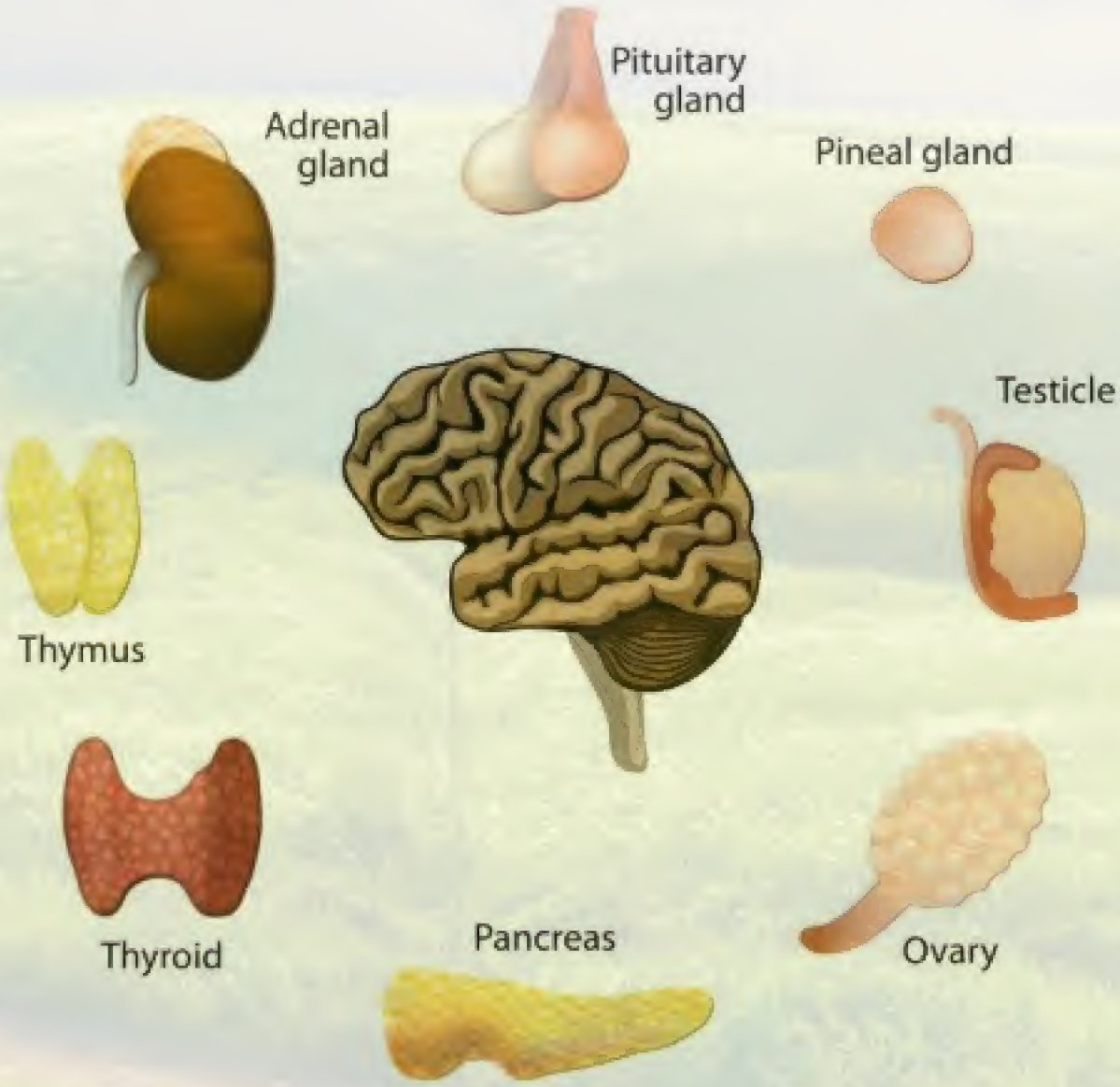
ENDOCRINE SYSTEM

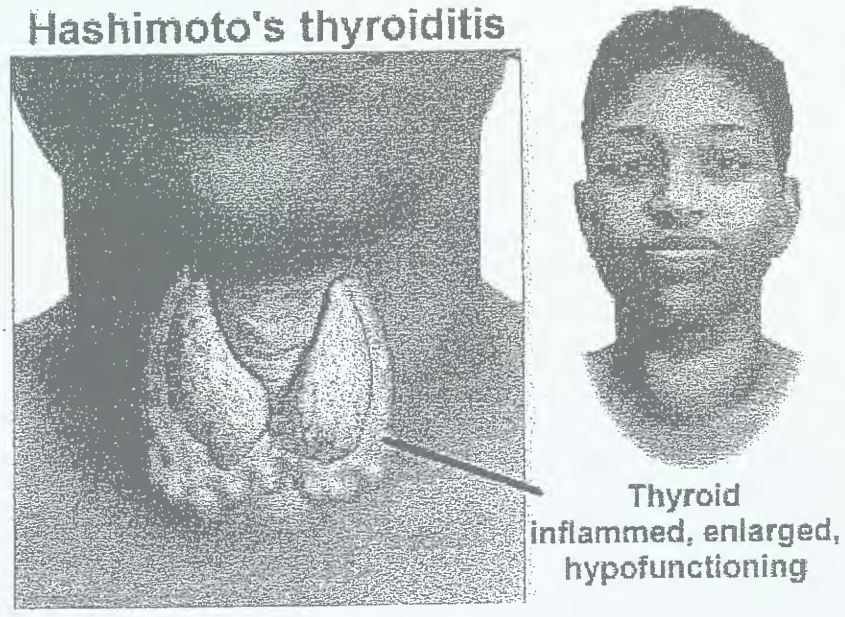


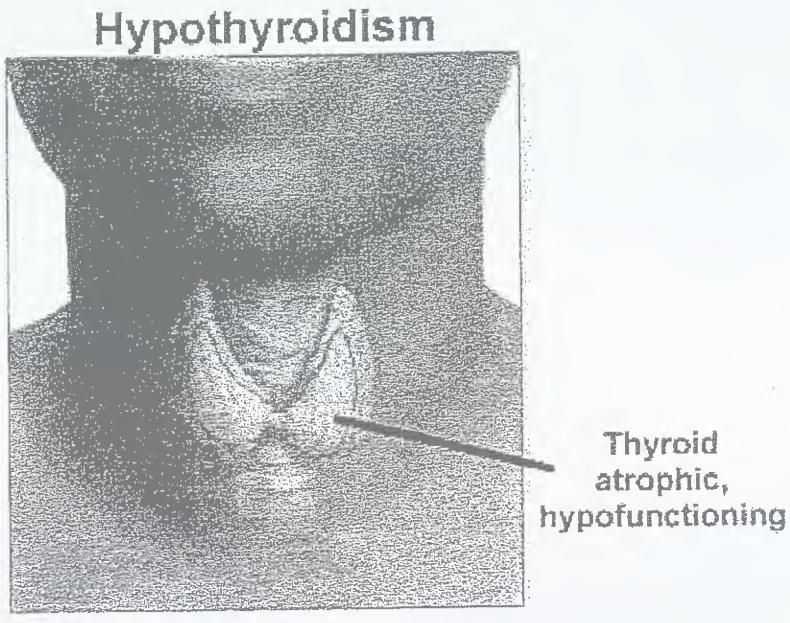
INDEX

MYXOEDEMA

FINITION

- Hypofunction of the thyroid gland; HYPOTHYROIDISM.





ETIOLOGY

I. PRIMARY MYXOEDEMA "Thyroid problem"

A) ACQUIRED HYPOTHYROIDISM

1. Inflammation: " Hashimoto's thyroiditis "

- *AUTOIMMUNE DISEASE.*
- *Associated with:*
  - Thyroid antibodies in 100 % of the cases.
  - Other autoimmune diseases, e.g. PA, SLE, RA, ITP.
- *Thyroid gland:*
  - Inflammation.
  - Enlargement: due to ↑ TSH secondary to ↓ thyroxin.

2. Idiopathic:

- *AUTOIMMUNE DISEASE.*
- *Associated with:*
  - Thyroid antibodies in 80 % of the cases.
  - Other autoimmune diseases, e.g. PA, SLE, RA, ITP.
- *Thyroid gland:*
  - Atrophic.

3. Iatrogenic:

- *Therapy for hyperthyroidism:*
  - Thyroidectomy,
  - Excessive radio-iodine therapy,
  - Prolonged use of antithyroid drugs.
- *Drugs:*
  - Amiodarone.
  - Lithium.
- *Irradiation:*
  - For lymphoma may damage the thyroid gland.

4. Iodine deficiency:

- Endemic myxoedema occurs due to prolonged iodine deficiency.

B) CONGENITAL HYPOTHYROIDISM.

II. SECONDARY MYXOEDEMA "Suprathyroid problem"

- The problem is not in the thyroid gland itself; the problem is suprathyroid:
  1. *Pituitary dysfunction.*
  2. *Hypothalamic dysfunction (Tertiary hypothyroidism).*

PATHOLOGY

1. There is *slowing of the cellular metabolic processes* due to ↓ thyroid hormones.
2. There is *accumulation of **m**ucopolysaccharide* in extracellular tissues:
   - Generalised thickening of the skin: nonpitting oedema *"**m**yxoedema"*.
   - Abnormalities in different tissues.

CLINICAL PICTURE

1. INCIDENCE

- *Sex:* more common in FEMALES.
- *Age:* 30 – 50 years.
- *Onset:* gradual.

2. GENERAL FEATURES

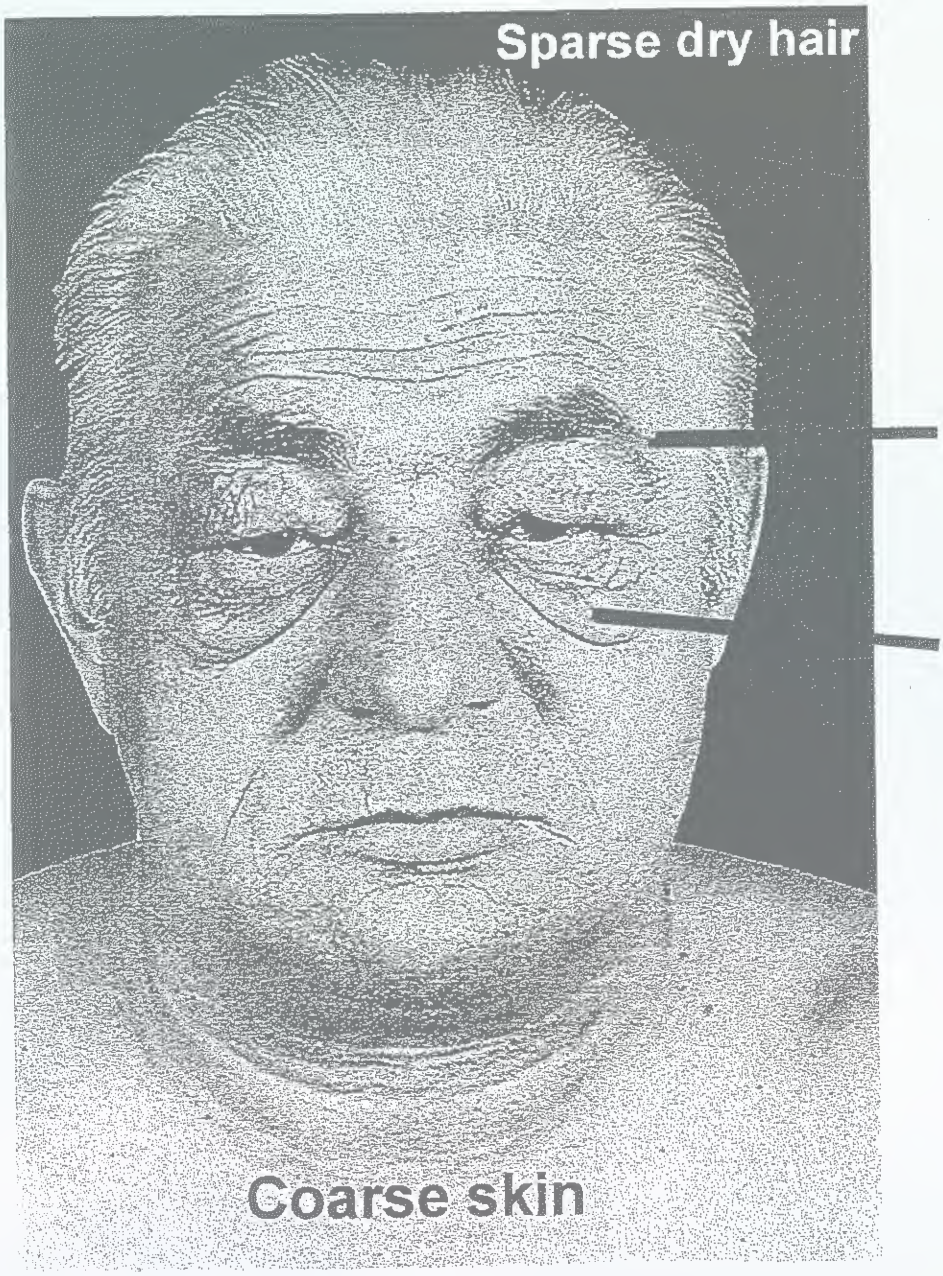
- **W**eakness, fatigue, tiredness, slow movement, somnolence.
- **W**eight gain.
- **W**eather: intolerance to cold, hypothermia.

3. FACE

- General look: face is *expressionless* & *bloated*.
- Eyebrows: sparse with loss of the outer third.
- Eyelids: puffy.
- Mouth: thickened lips & thickened tongue.

4. SKIN

- **C**old, dry (↓ sweating, ↓ activity of sebaceous glands).
- **C**oarse thickened: nonpitting oedema *"myxoedema"*.
- **C**olour: pale due to anemia & yellowish due to carotenemia.
- ***HAIR:*** sparse dry hair, or hair loss.



General look:

Expressionless
+
Bloated

Eye brow:

Sparse
+
Lost outer 1/3

Eye lid:

Puffy

5. CARDIOVASCULAR FEATURES

- *Pulse:* sinus bradycardia.
- *BP:* secondary hypertension.
- *Arteries:* atherosclerosis which may cause CAD, CVD, PAD.
- *Heart:* cardiomegaly due to CM, HF.
- *Pericardium:* pericardial effusion, & may be pleural effusion & ascites.

6. GENITAL FEATURES

- **G**alactorrhoea, *Menorrhagia & infertility*: in ♀.
- **G**ynecomastia: in ♂.

7. GIT FEATURES

- Slow motility → constipation OR **M**yxoedema megacolon.
- Slow absorption → malabsorption.

8. NEUROLOGICAL FEATURES

NEUROLOGICAL FEATURES OF MYXOEDEMA

- **M**ental impairment: poor memory, slow thinking, *APATHY*.
- **M**yxoedema madness: psychosis, depression.
- **M**yxoedema coma.
- **M**yopathy & peripheral neuropathy.
- **M**ucopolysaccharide accumulation:
  - In the vocal cords → hoarseness of voice.
  - In the internal ear → impaired hearing.
  - In the flexor retinaculum → carpal tunnel syndrome.
- DEEP REFLEXES: delayed relaxation of deep reflexes.

9. THE THYROID GLAND

- Inflammed, enlarged or there is a scar of thyroidectomy.

10. MYXOEDEMA COMA "*Hypothyroid or Hypothermic coma*"

- *Age:* more common in old patients.
- *Precipitating factors:* exposure to severe cold, infections.
- *Clinical picture:* confusion, then coma with:
  - **H**ypothermia.
  - **H**ypoventilation.
  - **H**ypoglycemia.
  - **H**eart failure.

INVESTIGATIONS

1. Thyroid function tests:

- T3 & T4 (total & free): ↓.
- **TSH:** ↑ *in primary* & ↓ *in secondary.*
- Thyroid radioactive I uptake: ↓.

↑ TSH in primary myxoedema is the most important investigation

2. Blood picture:

- *Normocytic anemia:*
- *Microcytic anemia:*
- *Macrocytic anemia:*

} Refer to "Hematology"

3. Biochemical changes:

- **S**erum cholesterol: elevated.
- **S**erum glucose: flat glucose tolerance curve.
- **S**erology: thyroid antibodies in *Hashimoto's* & *Idiopathic* thyroiditis.
- **S**GOT & CPK: may be elevated due to myopathy.

4. ECG:

- *Rhythm:* Sinus bradycardia.
- *Voltage:* Low voltage.
- *T wave:* Flat or inverted T wave.

- **Important question:** **"Self – assessment"**

"What is meant by Subclinical myxoedema" ??

DIFFERENTIAL DIAGNOSIS

1. Nephrotic syndrome.
2. Obesity.
3. Anemia.
4. Depression & psychosis.
5. Coma.
6. Polyserositis.
7. Differentiate between primary & secondary myxoedema.

TREATMENT

1. Replacement therapy (L – thyroxin): *"life long"*

- Start by: 50 µg / day.
- Increase the dose every one month by: 50 µg / day.
- Average maintenance dose: 200 µg / day.
- In old people & in patients with CAD:
  - Start by a lower dose (25 µg / day), & increase the dose very gradually to avoid precipitation of angina & HF.

MONTORING OF THERAPY

1. Clinical improvement.
2. Laboratory improvement:
   - Thyroid function tests (***TSH***, *free T3, T4*).
   - Cholesterol level.
   - ECG.

2. Treatment of myxoedema coma:

A) Replacement therapy:

- IV Hydrocortisone: 100 mg / 8 hours.
- IV Thyroxin: T3 5 µg / 8 hours, or T4 500 µg single dose.

B) Symptomatic ttt: "Care of the comatosed"

- For Hypothermia: Gradual rewarming.
- For Hyoventilation: Adequate oxygenation & ventilatory support.
- For Hypoglycemia: Dextrose infusion.
- For Heart failure: ttt of HF.

3. Treatment of subclinical myxoedema.

DISORDERS OF THE PITUITARY GLAND

I. DISORDERS OF THE ANTERIOR PITUITARY

1. *Hyperpituitarism:*

Excess secretion of	Disease
GH	Gigantism & Acromegaly
Prolactin	Galactorrhea
ACTH	Cushing's disease
TSH	Hyperthyroidism
MSH	Hyperpigmentation

2. *Hypopituitarism:*

a) In childhood:

i. *Pituitary dwarfism* (Levi-Lorain syndrome).

ii. *Frolich's syndrome.*

iii. *Laurance Moon Biedle syndrome.*

b) In adults:

i. *Isolated hormonal deficiency:*

- Decreased ACTH → Secondary adrenal failure.
- Decreased TSH → Secondary myxoedema.

ii. *Pan Hypopituitarism:* (Simmond's disease).

II. DISORDERS OF THE POSTERIOR PITUITARY

- Decreased ADH → Diabetes insipidus..
- Increased ADH → SIADH.

GIGANTASIM

ETIOLOGY

- Excessive secretion of GH ***"before fusion of the epiphysis"*** due to:
  - Pituitary hyperplasia: common.
  - Pituitary adenoma: rare.

CLINICAL PICTURE

A) ENDOCRINAL MANIFESTATIONS

1. Disproportionate gigantasim: span > height.
2. Later on: features of acromegaly occur.
3. Very late: fatigue & weakness occur due to pituitary insufficiency.

B) NEUROLOGICAL MANIFESTATIONS "*pressure manifestations*"

- Refer to "Brain tumours" in Neurology.

INVESTIGATIONS

- See investigations of Acromegaly.

DIFFERENTIAL DIAGNOSIS

- From other causes of: **" TALL STATURE "**:
  1. Familial & racial: proportionate gigantism.
  2. Primary hypogonadism: Disproportionate gigantism + feminine characters.
  3. Marfan's syndrome: *Aortic regurge, Mitral Regurge. Dislocation of the lens, Dislocation of the joints. High arched palate, Arachnodactyly.*

TREATMENT

- See treatment of Acromegaly.

ACROMEGALY

ETIOLOGY

- Excessive secretion of GH ***"after fusion of the epiphysis"*** due to:
  - Pituitary adenoma: common.
  - Pituitary hyperplasia: rare.

CLINICAL PICTURE

- *Age:* 20 – 40 years.
- *Onset:* gradual.
- *Course:* slowly progressive.

A) ENDOCRINAL MANIFESTATIONS

1. Head & face: *"Ape-like face"*

- **B**ig skull with elongated face.
- **B**ig ears, Big nose, Big lips, Big tongue.
- **P**rognathism + separation of the teeth.
- **P**rominent frontal bosses & prominent supraprbital ridges.

2. Hands: *" Spade-like hands"*

- **B**ig hands with blunt fingers.

3. Skeletal affection:

- Osteoarthritis may occur.

4. Skin affection:

- Thick, wrinkled, greasy.

5. Organ enlargement:

- **H**epatosplenomegaly.
- **H**eart enlargement *(with Cardiomyopathy)* → **H**F.
- **H**ypertrophy of the wall of the blood vessels → **H**ypertension.
- **H**ypertrophy of the larynx → **H**oarseness of voice.

6. Associated endocrinal disturbances:

- *Diabetes mellitus:* may occur in 30 % of the cases.
- *Galactorrhea:* may occur.

7. Muscle affection:

- Early: increased muscle power.
- Late: decreased muscle power & *MYOPATHY*.

B) NEUROLOGICAL MANIFESTATIONS

- **P**eripheral neuropathy.
- **P**arasthesias in hands & feet may occur due to:
  - *Peripheral neuropathy.*
  - *Diabetic neuropathy.*
  - *Carpal tunnel syndrome.*
- **P**ressure manifestations:
  - Refer to "Brain tumours" in Neurology.

INVESTIGATIONS

I. IMAGING

1. X-ray:

a) Skull:

- Thick cortex.
- Wide frontal sinuses.
- Prognathism + separation of the teeth.
- Sellar changes: enlargement of the sella turcica.

b) Hands:

- Phalanges: Broadening of the phalanges.
- Terminal phalanges: Tufting of the terminal phalanges (mushroom-like).

2. CT & MRI of the skull:

- For accurate diagnosis of pituitary tumours.

II. HORMONES

1. GH level in the serum:

- Increased (normally: < 5 ng / ml in adults).

2. Glucose suppression test:

- IV glucose fails to decrease GH level.

3. Prolactin level in the serum:

- Increased in 30 % of the cases.

III. BLOOD CHEMISTRY:

- Increased Ca, Increased Phosphates, Increased Glucose.

TREATMENT

1. Surgical ttt: *" Removal of the pituitary"*
   - Trans-sphenoidal.
   - Trans-frontal
2. Medical ttt:
   - Bromocriptine (30 mg / day): ↓ level of GH & ↓ size of the tumour.
   - Synthetic somatostatin (100 mcg / 8 h): *the drug of choice.*
3. Irradiation of the pituitary:
   - If surgical ttt is contraindicated.
   - If medical ttt gives no response.
4. Symptomatic ttt:
   - e.g. for *DM* & for *Hypertension.*

PAN HYPOPITUITARISM

(Simmond's disease)

ETIOLOGY

1. **P**ost-partum hemorrhage "Sheehan's syndrome": ***the most common cause***
   - Post-partum hemorrhage → VC & increased clotting tendency → thrombosis of the pituitary vessels → pituitary infarction.
2. **P**ituitary tumours.
3. **P**ituitary removal by surgery or pituitary irradiation.

CLINICAL PICTURE

I. EARLY FEATURES

- Insiduous onset of: weakness, apathy, weight loss.

II. DEFICIENCY FEATURES

1. Gonadal deficiency:

a) In females:

- Failure to establish lactation after delivery or infertility.
- Atrophy of the breasts, Amenorrhea.
- Loss of libido, Loss of pubic & axillary hair.

b) In males:

- Impotence.
- Loss of libido, Loss of pubic & axillary hair.

2. Thyroidal deficiency: *" Secondary myxoedema "*

- Clinical feaures of myxoedema.

3. Adrenocortical insufficiency: *" Secondary adrenal failure "*

- Clinical features of Addison's disease, BUT:
  - *Hyperpigmentation:* is absent.
  - *Hypotension:* is not severe due to continued release of aldosterone.

4. Pressure manifestations:

- In case of pituitary tumours.

II. LATE FEATURES

COMA may occur in late stages due to:

- Hypothermia.
- Hypoglycemia.

INVESTIGATIONS

1. IMAGING

- X-ray sella turcica.
- CT & MRI of the brain.

} **Evidence of Pituitary tumour**

2. HORMONES

A) ASSAY:

- Decreased GH.
- Decreased Prolactin.
- Decreased ACTH & Cortisol.
- Decreased TSH & T3 & T4.
- Decreased Gonadotrophines & Sex hormones.

B) COMBINED INSULIN TOLERANCE TEST:

- *Give:* IV INSULIN, followed by *TRH* & GnRH.
- *Normally:* marked ↑ in GH, ACTH, *TSH, Prolactin,* FSH, LH.
- *In Pan hypopituitarism:* no increase in these hormones.

DIFFERENTIAL DIAGNOSIS

1. Primary myxoedema "Thyroid myxoedema"
   - Features of myxoedema.
   - Hypogonadism: absent.
   - Body weight: markedly increased.
   - Investigations:
     - Gonadal & Adrenal functions: normal.
     - TSH: high.
2. Addison's disease: "Primary adrenal failure"
   - Features of Addison's disease.
   - Hyperpigmentation & Hypotension.
   - Diarrhoea.
   - Investigations:
     - Gonadal & Thyroid functions: normal.
     - ACTH: high.
     - ACTH administration: no effect.
3. Anorexia nervosa:
   - It usually occurs in: YOUNG WOMEN.
   - ANOREXIA + marked loss of weight.
   - AMENORRHEA + normal axillary & pubic hair.
   - Breasts: are well developed.
   - Thyroxin & cortisol levels are NORMAL.
4. Primary hypogonadism in males:
   - Features of hypogonadism.
   - Disproportionate gigantism: if the condition starts in childhood.
   - Thyroxin & cortisol levels are NORMAL.

TREATMENT

1. Treatment of the cause, if possible.
2. Hydrocortisone: 30 mg / day.
3. Thyroxin:
   - It should be given after hydrocortisone, to avoid acute adrenal insufficiency.
   - It should be given in a small dose, followed by very gradual increase of the dose.
4. Gonadal hormones:
   - *In females:* diethylstilbestrol.
   - *In males:* methyl testosterone.

DWARFISM

(Stunted growth - Short stature)

A) Endocrinal diseases

1. Hypothalamic syndromes:

   a. *Frohlich's syndrome:*
      - Trunkal obesity, hypogonadism, genu-valgum.

   b. *Laurance Moon Biedle syndrome:*
      - Trunkal obesity, hypogonadism, genu-valgum.
      - Polydactyly, mental retardation, retinitis pigmentosa.

2. Cretinism:
   - Disproportionate dwarfism + features of cretinism.

3. Pituitary dwarfism "Levi-Lorain syndrome"
   - Proportionate dwarfism + hypogonadism.

4. Precocious puberty:
   - Increased secretion of sex hormones causes premature fusion of the epiphysis.

5. IDDM.

B) Severe chronic illness during childhood

1. *Cardiac*: Congenital, Rheumatic valvular.
2. *Chest*: Cystic fibrosis, Severe bronchial asthma.
3. *Liver*: Lipid & glycogen storage disease, Veno-occlusive disease.
4. *GIT*: Malnutrition, Malabsorption.
5. *Renal*: Chronic renal failure.
6. *Blood*: Chronic severe anemia.
7. *Chronic infections*: e.g. TB.

C) Skeletal causes

1. Achondroplasia:
   - Limbs: Short.
   - Trunk: Normal.

2. Osteochondrodystrophy:
   - Limbs: Short & deformed.
   - Trunk: Short & deformed.

3. Osteogenesis imperfecta:
   - BONES: Fragile bones → multiple fractures → malunion → dwarfism.
   - EYES: Blue sclera.
   - EARS: Conductive deafness.

4. Rickets.

5. Pott's disease of the spine.

D) Genetic diseases

1. Laurance Moon Biedle syndrome.

2. Mongolism.

3. Turner's syndrome: *primary amenorrhea*, *sexual infantilism*, *short stature*.

4. Progeria: *premature senility*.

E) Familial & racial.

DIABETES MELLITUS

DEFINITION

- A chronic disorder characterized by impaired glucose metabolism → **HYPERGLYCEMIA**.
- It is associated with secondary changes in multiple organs → COMPLICATIONS.
- It is due to: *Insulin deficiency.* *Insulin resistance* OR *Both.*
- INCIDENCE: It is the most common endocrine disease, 1 – 2 % in most of the communities.

ETIOLOGY & PATHOGENESIS

1. PRIMARY DIABETES (> 95 % of DM)

TYPE I Insulin Dependent Diabetes Mellitus (IDDM)

- It is also described as: " Ketoacidosis prone".
- It was previously termed: " Juvenile-onset diabetes ".
- It **essentially** depends on: INSULIN in its treatment.

- **Predisposing factors:**

1. *Genetic factors:*
   - There is association with certain HLA types.
   - There is 50 % incidence in identical twins.
   - There is ↑ risk of inheritance: ***30 % if both parents are diabetic.***
2. *Immunological factors*
   - Immunologic markers: Islet Cell Abs (ICAs) & Anti-insulin Abs.
   - INSULITIS: Infiltration of pancreatic islets with LYMPHOCYTES.
   - Associated AI diseases: ***e.g.*** *Coeliac dis, Grave's dis, Addison's dis.*

TYPE I DM is further divided into 2 subtypes:

- Type I A: Immune-mediated ß cell destruction with ***presence*** of Immunologic markers.
- Type I B: Idiopathic ß cell destruction with ***absence*** of Immunologic markers.

3. *Environmental factors:* **"Triggers"**
   - They trigger the autoimmune process: in the genetically susceptible individuals.
   - The most important factors are: Viral infection *(Coxsackie & Rubella).*

- **Insulin abnormality:**
  - INSULIN DEFICIENCY: secondary to destruction of the ß - cells.

TYPE II Non – Insulin Dependent Diabetes Mellitus (NIDDM)

- It is also described as: " Ketoacidosis resistant".
- It was previously termed: " Maturity-onset diabetes ".
- It does not **essentially** depend on: INSULIN in its treatment.

- **Predisposing factors:**

1. *Genetic factors:*
   - There is no association with certain HLA types.
   - There is 100 % incidence in identical twins.
   - There is ↑ risk of inheritance: ***40 % if both parents are diabetic.***

2. *Obesity:*
   - It is absent in: 20 % of the patients (Type II A).
   - It is present in: 80 % of the patients (Type II B).
   - INSULIN RESISTANCE: due to secretion of Leptin & FFAs.

- **Insulin abnormality:**

1. INSULIN RESISTANCE: " IR "
   - Decreased insulin action on target tissues : (muscle & liver) due to:
     - ***Receptor defect:*** ↓ insulin **receptors** in target tissues *(Minor role).*
     - ***Postreceptor defect:*** in target tissues *(Major role).*

2. IMPAIRED INSULIN SECRETION:
   - ***Initially:***
     ↑ **insulin secretion occurs due to IR to maintain normal glucose "Hyperinsulinemia".**
   - ***Later:***
     ↓ **insulin secretion occurs due to islet cell failure secondary to "Glucose toxicity".**

3. INCREASED HEPATIC GLUCOSE PRODUCTION:
   - IR → failure of insulin to suppress gluconeogenesis → Fasting hyperglycemia.

	Type 1	Type 2
Incidence	10 %	90 %
Age of onset	Less than 30	More than 30
Body weight	Usaually decreased	Usually increased
Severity	More severe	Less severe
Complications	More common	Less common
Coma	DKA	Hyperosmolar coma
Insulin level	Low or absent	High (early), low (later)
Insulin therapy	Always essential	Not always essential
Oral hypoglycemic drugs	Not effective	Effective

SPECIAL TYPES

Maturity Onset Diabetes of the Young (MODY)

A subtype of type 2 diabetes, but the main defect is impaired insulin secretion & not IR.

- **Etiology:** GENETIC defects in **insulin secretion:**
  (6 variants: MODY 1, **2,** 3, 4, 5, 6 due to mutations in 6 genes).
- **Onset:** YOUNG, Early onset of Hyperglycemia:
  (Between: 10 – 25 years).

Latent Autoimmune Diabetes of the Adult (LADA)

A subtype of type 1 diabetes, but autoimmune ß – cell destruction is slow.

- **Etiology:** AUTOIMMUNE ß – cell destruction.
- **Onset:** ADULT, Late onset of Hyperglycemia:
  (Above: 30 years).

BRITTLE DIABETES

- A type of diabetes with wide unpredictable fluctuations in blood glucose levels.
- Also called: unstable diabetes or labile diabetes.

2. SECONDARY DIABETES (< 5 % of DM)

1. Pancreatic exocrine diseases:

- Chronic pancreatitis, Cancer pancreas, Cystic fibrosis.
- Hemochromatosis, Pancreatectomy.

2. Endocrinal diseases: "Increased Anti – insulin hormones"

- Increased GH: *Acromegaly.*
- Increased Glucagon: *Glucagonoma.*
- Increased Catecholamines: *Pheochromocytoma.*
- Increased Cortisol: *Cushing's syndrome.*
- Increased Thyroxin: *Thyrotoxicosis.*

3. Renal diseases: Chronic renal failure.

4. Liver disease: Chronic liver failure.

5. Drugs:

- Corticosteroids, Thyroid hormone.
- Diazoxide, Diuretics *(Thiazides, Frusemide).*

6. GESTATIONAL DM:

- IGT: first detected during LATE PREGNANCY (2^{nd} or 3^{rd} Tri).
- Etiology: IR + ↑ secretion of Anti – insulin hormones in late preg.
- Incidence: 2 % of pregnant women.
- COURSE:
  - *Usually: reverts to normal after delivery.*
  - *In 40 %: passes to Type 2 diabetes within 5 – 10 years.*

CLINICAL PRESENTATIONS

1. Asymptomatic: *Accidentally discovered.*
2. Symptomatic: 5 **P**
   - **P**olyuria, **P**olydipsia, **P**olyphagia, **P**ruritus, **P**arasthesia.
   - Loss of weight: *in type 1 diabetes.*
3. Complications: affecting multiple organs **or** acute complications (coma).
4. Cause: in case of secondary diabetes.

CRITERIA FOR DIAGNOSIS OF DM

1. FPG: ≥ 126 mg / dL on at least 2 separate occasions.
2. Two-hour PG: ≥ 200 mg / dL during an OGTT.
3. Symptomatic DM: **plus** RPG ≥ 200 mg / dL.

CRITERIA FOR DIAGNOSIS OF IFG & IGT

1. IFG: FPG is: 110 – 126 mg / dL on at least 2 separate occasions.
2. IGT: Two-hour PG is: 140 – 200 mg / dL during an OGTT.

- *Both: represent a state of Hyperglycemia but do not meet the criteria for diagnosis of DM.*
- *Both: do not produce classic symptoms or complications of DM.*
- *Both: are at risk for developing Type 2 DM (25 %).*

INVESTIGATIONS

1. Plasma glucose: " Fasting & 2 hours post prandial "

- *Normal levels:*
  - FPG: 70 – 110 mg / dL
  - Two-hour PG: less than 140 mg / dL.
- *Abnormal levels:*
  - Diagnosis of DM: see before.
  - IFG & IGT: see before.

2. Oral Glucose tolerance test: (OGTT)

- Fasting blood & urine are collected & measured for glucose.
- The patient is given 75 gm glucose in 300 ml water orally.
- Blood & urine are collected & measured for glucose every ½ hour for 2 hours.

3. Urine analysis:

- To detect: glucose or acetone in urine.

4. Monitoring of treatment:

- ***Plasma glucose monitoring.***
- ***Glycosylated hemoglobin:*** (Hb-A1c)
  - Formation: by linkage of glucose to ß chains of Hemoglobin A.
  - Normal level: 6 % of the total hemoglobin.
  - Value: *estimates the efficiency of DIABETIC CONTROL during the preceding several weeks (6 – 12 weeks).*

5. Investigations for: Complications, Cause *(in secondary diabetes)*.

COMPLICATIONS

I. CARDIOVASCULAR

1. Macrovascular complications: " Atherosclerosis "

- CAD: Angina, AMI (may be painless), HF, Sudden death.
- CVD: Stroke (cerebral thrombosis → hemiplegia).
- PAD: Ischemia of LL (intermittent claudications & gangrene).

2. Microvascular complications: " Microangio***pathy*** "

- Neuro***pathy***.
- Retino***pathy***.
- Nephro***pathy***.

3. METABOLIC SYNDROME: " Syndrome X "

- HYPERTENSION.
- IR → HYPERGLYCEMIA *(IFG or IGT or Diabetes).*
- OBESITY, esp. abdominal *(excessive fat around the abdomen).*
- Atherogenic DYSLIPIDEMIA ***(high TG, low HDL*** *& high LDL).*

ATHEROSCLEROSIS IN DIABETES

1. Dyslipidemia.
2. Endothelial dysfunction.
3. ↑ liability to HTN.
4. ↑ Cytokines → ↑ growth factors → accelerated atherosclerosis.
5. Prothrombotic state: ↑ fibrinogen, vWF, PAI-1 & ↑ platelet aggregation.

HTN IN DIABETES

1. Endothelial dysfunction.
2. Insulin resistance.
3. Diabetic nephropathy.

II. NEUROLOGICAL

1. Cerebral complications: "emergencies"
   - COMA: of different types, " see later ".
   - CVD: Stroke (cerebral thrombosis → hemiplegia).
   - INFECTIONS: fungal (rhinocerebral mucormycosis).
2. Spinal cord complications: "rare"
   - Posterior column affection: Sensory ataxia.
   - Pyramidal tract affection: Diabetic lateral sclerosis.
3. Root complications:
   - Radiculitis: esp. affecting the roots of sciatic nerve (SCIATICA).
     - *Posterior root: pain & parasthesia, then, sensory loss.*
     - *Anterior root: weakness & wasting.*
4. Peripheral neuropathy:
   - Refer to " neurology ".

III. GIT

1. Mouth: *Dental caries, gingivitis, loosening of teeth.*
2. Stomach: *Gastroparesis* + N, V & acute abdominal pain during DKA.
3. Intestine: *Diarrhoea.*
4. Liver: *Fatty liver.*
5. GB: *Chronic cholecystitis & gall stones are common.*

IV. RESPIRATORY

1. INFECTIONS: especially TB & Pneumonias.
2. During DKA: (Breath problems)
   - *Rapid deep breathing (Kussmaul's breathing)*
   - *Acetone odour in the breath.*

V. GENITAL

1. Males: *Impotence.*
2. Females:
   - INFECTIONS: *vaginal moniliasis.*
   - Pruritus vulvae.

DIABETES & PREGNANCY

I. Effects of DM on pregnancy:

On mother:
- Post- partum hemorrhage & puerperal sepsis.
- Premature labour, abortion, eclampsia.

On fetus:
- Congenital anomalies.
- Delivery of BIG BABIES.

II. Effects of pregnancy on DM:
- Gestational DM.
- Increased incidence of DKA.

VI. OCCULAR

1. Errors of refraction.
2. Cataract.
3. Glaucoma: *due to Rubiosis iridis (new vessel formation in the iris).*
4. INFECTIONS: **e.g.** *blepharitis & panophthalmitis.*
5. Nervous: *paralysis of the ocular nerves, esp. 3rd nerve.*
6. DIABETIC RETINOPATHY:
   - Simple (Background) retinopathy: *harmless.*
   - Proliferative retinopathy: *neovascularization, VH, RD.*
   - Exudative retinopathy: *macular oedema.*

VII. CUTANEOUS

1. Pruritus:

- Especially pruritus vulvae: *due to monilial infections & parasthesia.*

2. INFECTIONS:

- Multiple furuncles: & carbuncles.
- Abscesses: & cellulitis.
- Fungal infections: *especially in the ano-genital region & interdigital.*

3. Diabetic dermopathy:

- Nature: *Red painless **papules**.*
- Site: over the shins of tibiae & may ulcerate.
- Cause: occlusion of the cutaneous blood vessels.

4. Necrobiosis diabeticorum:

- Nature: *Red painless **papules with yellow center**.*
- Site: over the shins of tibiae & may ulcerate.
- Cause: microangiopathy & fat deposition.

5. Acanthosis nigricans:

- Nature: Hyperpigmented (brown to black) velvety patches.
- Site: over the neck, axilla or ano – genital region.
- Cause: insulin spillover into the skin (due to excess insulin in IR).

People with acanthosis nigricans should be screened for diabetes

6. Delayed healing of wounds.

7. Xanthomata: *yellow plaques around the eye lids due to hyperlipidemia.*

8. Carotinemia: *yellow discolouration of skin due to ↑↑ intake of vegetables.*

9. Cutaneous features of DIABETIC FOOT.

10. Complications of ttt: **e.g.** *insulin lipodystrophy (see ttt).*

VIII. RENAL

1. Infections:

- Urethritis, Cystitis.
- Pyelonephritis: complicated by *ACUTE NECROTIZING PAPILLITIS*.

2. Stones:

- More common than in normal persons.

3. Diabetic nephropathy: " Diabetic glomerulosclerosis "

- **Pathology:**
  - Thickening of the BM of the glomeruli.
  - Deposition of hyaline material (sclerosis) in the glomeruli " **KW deposits** ".
  - Disruption of part of the membrane → excessive leak of proteins.

- **Clinical picture:** " Kimmelstiel – Wilson syndrome "
  - Early: **asymptomatic** with **microalbuminuria**.
  - Later: persistent heavy proteinuria & **nephrotic syndrome**
  - Latest: ↓ GFR, ↑ serum creatinine & **renal failure.**
  - **Hypertension:** is common & it causes more renal damage.
  - **Diabetic retinopathy:** usually precedes the development of nephropathy.

- **Treatment:**
  - Early: detection of **microalbuminuria** & slowing its progression to nephropathy:
    - Strict control of DM & HTN (130 / 80).
    - ACE inhibitors.
  - Later: with the onset of persistent heavy proteinuria & **nephrotic syndrome**:
    - Strict control of DM & HTN (130 / 80).
    - ACE inhibitors or ARBs.
  - Latest: with development of **renal failure**:
    - TTT as in uremia: renal transplantation or dialysis.

IX. ACUTE COMPLICATIONS

" see later."

TREATMENT OF DM

LINES OF TREATMENT

I. DIET TREATMENT.
II. ORAL HYPOGLYCEMIC DRUGS.
III. INSULIN.
IV. NEW LINES OF TTT.
V. TTT OF COMPLICATIONS.
VI. TTT OF THE CAUSE.
VII. TTT OF SPECIAL SITUATIONS.

DIET TREATMENT

CONCEPT

- To keep caloric supply in a range compatible with endogenous insulin.

CALCULATION OF DAILY CALORIES

- For underweight patients: 40 cal / Kg / day.
- For average weight patients: 30 cal / Kg / day.
- For overweight patients: 20 cal / Kg / day.

CHOICE OF DAILY CALORIES

- Carbohydrates: 50 % of calories.
- Fats: 30 % of calories.
- Proteins: 20 % of calories.

CHOICE OF CARBOHYDRATES

- Avoid simple sugars: because they are rapidly absorbed.
- Allow complex sugars: because they are slowly absorbed.

CHOICE OF MEALS

- Advise food rich in fibres (e.g. bran), because fibres will slow sugar absorption.
- Advise frequent small meals:
  - *To avoid hypoglycemic attacks with insulin & oral ttt.*
  - *To avoid hyperglycemic peaks with large meals.*

II. ORAL HYPOGLYCEMIC DRUGS

1. Sulphonylureas

" *Insulin secretagogues* "

ACTION

- Decrease insulin resistance.
- Increase insulin secretion from the pancreas: MAIN ACTION.
- Decrease hepatic glucose production.

INDICATIONS

- NIDDM: *not controlled on diet ttt.*

CONTRAINDICATIONS

- IDDM.
- NIDDM: with severe hyperglycemia.
- *DKA.*
- *Diabetes with pregnancy.*
- **S**urgery.
- **S**evere **liver disease** or **renal disease.**

PREPARATIONS

Drugs	Daily dose in mg	Duration of action, hours
First generation drugs		
Chlorpropamide	100 – 500	24 – 48
Tolazamide	100 – 1000	12 – 24
Tolbutamide	500 – 3000	6 – 12
Second generation drugs		
Glimepride	1 – 8	24
Glibenclamide	5 – 15	12
Glipizide	2.5 – 40	12
Gliclazide	80 – 320	12

NB Second generation drugs are preferred because of shorter duration of action and therefore *less incidence of hypoglycemia.*

SIDE EFFECTS

- HYPOGLYCEMIA: *especially with first generation drugs.*
- BM: depression, *especially with Chlorpropamide.*
- GIT: irritation.
- Skin: rash.

2. Biguanides

ACTION

- Increase: passage of glucose into the cells.
- Increase: anaerobic glycolysis.
- Decrease: appetite.
- Decrease: glucose absorption.
- Decrease: gluconeogenesis.

INDICATIONS

- Obese NIDDM (Type II B): *not controlled on diet ttt.*

CONTRAINDICATIONS

- Same as: Sulphonylureas.

PREPARATIONS

- Metformin: 500 mg tds.
- Phenformin: 25 mg tds *(not used now).*

SIDE EFFECTS

- Appetite: *loss.*
- GIT: *irritation.*
- Lactic acidosis.
- Homocysteinemia.
- Anemia: *due to vitamin B12 malabsorption.*
- ALONE: THEY DO NOT CAUSE HYPOGLYCEMIA.

3. New oral hypoglycemic drugs

a) Alpha – Glucosidase inhibitors: e.g. *Acarbose.*
   - Decrease post prandial hyperglycemia by: delaying glucose absorption.

b) Benzoic acid derivatives: e.g. *Repaglinide.*
   - Increase INSULIN SECRETION.

c) Insulin sensitizers: **" Thiazolidine-diones "** e.g. *Rosiglitazone & Pioglitazone.*
   - Decrease INSULIN RESISTANCE (PPARγ agonists).

d) Incretin enhancers: **" DPP – 4 inhibitors "** e.g. *Sitagliptin.*
   - Prevent degradation of incretins → beneficial actions on glucose regulation.

III. INSULIN

INDICATIONS

- IDDM.
- NIDDM: with severe hyperglycemia not controlled by diet & OHD.
- *DKA.*
- *Diabetes with pregnancy.*
- **S**urgery.
- **S**evere **liver disease** or **renal disease.**
- **S**evere **stress:** infection.

ORIGIN

- Animal insulin: from cows or pigs ..... rarely used now.
- Human insulin: genetic engineering ..... widespread use now: *most powerful*, *least allergic*.

PREPARATIONS

Insulin	Onset	Peak	Duration
Short acting			
Crystalline (regular)	½	3	6
Semilente	1	6	12
Intermediate acting			
Isophane (NPH)	3	8	24
Lente	3	8	24
Long acting			
Protamine zinc insulin	4	16	36
Ultralente	4	16	36
Mixtures	Mixtard: 30 / 70 &		Initard: 50 / 50

DOSE

- The ttt is usually started with 20 units / day in average weight patients.
- The dose is gradually increased (e.g. by 5 – 10 units / day) until blood glucose is controlled.

ADMINISTRATION

A SUBCUTANEOUS: *Many methods could be used, e.g.*

1. Single injection before breakfast:
   - Short acting (30 % of the required dose) + long acting (70 % of the required dose).
2. Twice daily injections:
   - Morning injection: 2/3 of the total daily dose.
   - Evening injection: 1/3 of the total daily dose.
3. Multiple daily injections: " *in cases of poor glycemic control* "
   - Regular insulin before each meal + evening long acting insulin.

   NB Injections can be given by insulin syringes or by pen injection devices.
4. Continuous Subcutaneous Insulin Infusion: Insulin pump.

   They deliver: ***rapid-onset, short-acting insulin*** 24 hours a day,
   Through a: ***catheter placed under the skin.***

   DOSES:
   - **B**asal (small) dose: delivered constantly.
   - **B**olus dose: delivered with meals.

   ADVANTAGES:
   - Eliminates the need for injections.
   - Delivers insulin more accurately than injections.
   - Decreases the fluctuations in blood glucose levels.

   DISADVANTAGES:
   - Expensive.
   - Inconvenient.
   - DKA: *if the catheter comes out & there is no insulin for hours.*

B IV infusion or IM: *In case of DKA or Hyperosmolar coma.*

C Insulin spray *(Nasal or Oral)*: *New.*

D Oral insulin: *Investigational.*

COMPLICATIONS

1. HYPOGLYCEMIA.
2. Weight gain.
3. Insulin lipodystrophy: atrophy of SC fat at sites of injections forming skin dimples.
4. Allergic reactions: *least with human insulin*.
5. Insulin resistance: *due to:*
   - Antibodies against insulin preparations *(least with human insulin)*.
   - Obesity.
6. Insulin in a **wrong dose**: " Night Dose "
   - Dawn phenomenon: morning hyperglycemia due to **under dosage** of insulin.
   - Somogyi effect: morning hyperglycemia following nocturnal hypoglycemia due to **over dosage** of insulin.

HONEYMOON PHASE

- A TEMPORARY phase in the first 1 – 2 years after the onset of TYPE I DM.
- **Reduction in exogenous insulin needs due to temporary improvement in ß cell function.**
- Blood glucose is controlled with very small doses of insulin.

IV. NEW LINES OF TTT

- Pancreatic transplantation.
- Pancreatic islet cells transplantation.

V. TTT OF COMPLICATIONS

e.g. TTT of diabetic nephropathy: see before.

e.g. TTT of different types of coma: see later.

VI. TTT OF CAUSE (in secondary D)

e.g. TTT of CRF.

VII. TTT OF SPECIAL SITUATIONS

1. TTT OF DM DURING *PREGNANCY*

a) **General:**

Daily home blood glucose monitoring + outclinic assessment every 2 weeks.

b) **Investigations:**

Fundus exam. + urinary protein at first, at 28 weeks & before delivery, because *retinopathy & nephropathy* may deteriorate during pregnancy.

c) **Control:**

By diet ttt, *if not enough,* give insulin.
Oral hypoglycemic drugs are contraindicated.

2. TTT OF DM DURING *SURGERY*

a) **Two days before surgery:**

Stop: oral hypoglycemic drugs.

b) **One day before surgery:**

Stop: long acting insulin & replace by: short acting insulin.

c) **On the surgery day:**

Give: infusion of glucose, short acting insulin & K.

d) **After surgery:**

Maintain: the infusion until the patient is allowed to eat.

e) **Monitoring:**

Check: glucose & K levels every *4 hours*.

- **Important question:** **"Self – assessment"**

"What are stepwise guidelines for the management of type 2 Diabetes ??"

COMA IN DM

I. DIABETIC KETOACIDOSIS (DKA) "Diabetic coma"

- DKA is the hallmark of TYPE I DM.

ETIOLOGY

- **S**toppage of insulin intake **(missed insulin)**.
- **S**evere hyperglycemia (inadequate ttt).
- **S**tress of a precipitating factor: *which needs high energy as in:*
  - Psychological stress.
  - Pregnancy, labour.
  - Stroke, AMI.
  - Surgery, Infection, Trauma.

PATHOGENESIS

1. Insulin: very low → hyperglycemia → osmotic diuresis → **Dehydration**.
2. Fats: Lipolysis to produce energy → ↑↑ ketone bodies which will cause:
   - Ketonemia → **Metabolic acidosis**.
   - Ketonuria → acetone in urine.
3. Potassium: **Hyperkalemia** occurs due to extracellular shift of K secondary to:
   - Insulin deficiency.
   - Acidosis.
4. COMA: due to the combined effect of:
   Dehydration, **Acidosis**, & **Hyperkalemia**: on the BRAIN.

CLINICAL PICTURE

1. General: Slow onset with marked Polyuria + Polydipsia.
2. GIT: Dyspepsia, nausea, vomiting, + acute abdominal pain.
3. Breath: Rapid deep breathing (Kussmaul's) + acetone odour.
4. Brain: Confusion, then Coma.
5. Dehydration: Dry skin, dry tongue, sunken eyes, + weak rapid pulse, ↓ BP.

INVESTIGATIONS

1. Blood: Glucose is markedly increased.
2. Urine: Glucose & acetone appear in urine.
3. Serum K: Increased (extracellular shift).
4. pH: Decreased.

TREATMENT

1. HOSPITALIZATION: better in an ICU.

2. INSULIN:

- ***Type:*** short acting insulin.
- ***Route:***
  - During ketosis: IV infusion, or repeated IM.
  - After disappearance of ketosis: Multiple daily SC injections.
- ***Dose:***
  - 6 – 10 units / hour: until ketosis disappear.
  - Larger doses (12 – 20 units / hour): may be used in resistant cases.

3. IV FLUIDS:

- ***Amount required:*** usually 4 – 8 litres.
- ***Type:***
  - Start by normal saline as follows:
    1 litre in ½ hour, followed by:
    1 litre in 1 hour, followed by:
    ½ litre every hour until the deficit is replaced.
  - Then give 5 % glucose solution:
    When blood glucose drops to 250 mg / dl: *to avoid hypoglycemia.*

4. CORRECTION OF ACIDOSIS:

- IV infusion of sodium bicarbonate: in severe acidosis (pH < 7.1).

5. POTASSIUM: *Should be given because:*

- Hypokalemia occurs during ttt due to intracellular shift of K secondary to:
  - Insulin therapy.
  - Correction of Acidosis.
- Dose: 20 – 40 mEq of K added to each litre of infusion.

6. TTT OF THE PRECIPITATING FACTORS:

- e.g. Antibiotics for infection.

7. MONITORING OF THE PATIENT

- ***Clinically:***
  - Level of consciousness.
  - Signs of dehydration.
  - PULSE, BP & CVP.
- ***Laboratory:***
  - Blood: Glucose.
  - Urine: Glucose & acetone.
  - Serum K.
  - pH.

II. HYPOGLYCEMIC COMA

ETIOLOGY

1. Over dose of insulin or sulphonylurea.
2. Diminished carbohydrate intake following ttt: **missed meal**.

PATHOGENESIS

1. Coma: due to ↓ energy supply to the brain secondary to hypoglycemia.
2. Adrenaline: is secreted to ↑ glucose production in the liver (glycogenolysis).
3. Hyperadrenalism: occurs & causes stimulation of the sympathetic system.

CLINICAL PICTURE

- There are features of: " ***Sympathetic over activity*** "
  - Symptoms: Rapid onset of *Irritability, tremors, pallor, sweating, palpitation.*
  - Signs: Dilated pupils, moist skin, strong rapid pulse, ↑ BP.
  - Course: Convulsions, Coma, Brain damage & death in severe cases.
  - Response to ttt: Rapid response to IV or oral glucose.

INVESTIGATIONS

1. Blood: Glucose is markedly decreased (< 50 mg / dl).
2. Urine: No glucose in urine.

TREATMENT

1. In severe hypoglycemia: IV glucose & IV glucagon (in resistant cases).
2. In early hypoglycemia: oral glucose.

	DKA	Hypoglycemia
1. History	Missed insulin	Missed meal
2. Onset	Slow	Rapid
3. Coma	Silent	Irritable
4. Skin	Dry	Moist
5. Tongue	Dry	Moist
6. Eyes	Sunken	Normal
7. Pupils	Normal	Dilated
8. Breathing	Kussmaul's	Normal
9. Breath	Acetone odour	Normal
10. Pulse	Weak & rapid	Strong
11. BP	Low	High
12. Urine	Glucose & acetone	Normal
13. Blood glucose	Very high	Low
14. Response to glucose	No effect	Rapid improvement

III. HYPEROSMOLAR NON-KETOTIC COMA

Severe hyperglycemia without ketosis, usually in a *neglected elderly TYPE 2 DM*.

ETIOLOGY

1. Uncontrolled Type 2 DM: with severe hyperglycemia.
2. A precipitating factor such as: *Stroke, AMI, or infection.*

PATHOGENESIS

1. Insulin deficiency is less severe in Hyperosmolar coma than in DKA.
2. Low endogenous insulin → hyperglycemia → osmotic diuresis → **Dehydration**.
3. Low endogenous insulin: is sufficient to inhibit ketogenesis → **no Acidosis**.

CLINICAL PICTURE

" ***Dehydration with no acidosis*** "

1. General: Slow onset with marked Polyuria + Polydipsia.
2. Brain: Confusion, then Coma.
3. Dehydration: Dry skin, dry tongue, sunken eyes, + weak rapid pulse, ↓ BP.

INVESTIGATIONS

1. Blood: Glucose is markedly increased, ↑ Na (due to dehydration).
2. Urine: Glucose appears in urine, BUT no acetone.

TREATMENT

1. Hospitalization: better in an ICU.
2. IV fluids: using normal saline " ***The most important measure*** ".
3. Insulin: as in DKA.
4. Potassium: as in DKA.
5. ***Na Bicarbonate:*** ***is not given***.
6. TTT OF THE PRECIPITATING FACTORS: e.g. *Antibiotics for infection.*
7. Monitoring the patient: as in DKA.

IV. LACTIC ACIDOSIS COMA

ETIOLOGY

- It occurs in diabetics using BIGUANIDES.
- It may be precipitated by TISSUE HYPOXIA, e.g. *HF, shock, resp. failure.*
- BIGUANIDES or TISSUE HYPOXIA → Anaerobic glycolysis.
- Anaerobic glycolysis → accumulation of lactic acid → severe **Acidosis.**

CLINICAL PICTURE

" Acidosis with no dehydration "

1. *B*reath: Rapid deep breathing (Kussmaul's).
2. *B*rain: Confusion, then Coma.

INVESTIGATIONS

- pH: ↓.

TREATMENT

- IV sodium bicarbonate.

HYPERPARATHYROIDISM

DEFINITION

Hyperparathyroidism is overactivity of the parathyroid glands resulting in: excess production of parathyroid hormone (**PTH**).

ETIOLOGY

1. Primary Hyperparathyroidism

- It results from a hyperfunction of the parathyroid glands themselves:
  - Most commonly **adenoma**, Rarely carcinoma.
  - MEN: 1, 2 A.
- Serum Ca: ↑, PTH: ↑.

2. Secondary Hyperparathyroidism

- It is a reversible compensatory ***hyperplasia*** of the parathyroid glands due to hypocalcemia caused by something other than a parathyroid pathology; e.g. CRF or Malabsorption syndrome.
- Serum Ca: low or normal, PTH: ↑.

3. Tertiary Hyperparathyroidism

- It is an ***irreversible parathyroid hyperplasia*** after longstanding secondary hyperparathyroidism.
- Serum Ca: ↑, PTH: ↑.

4. Pseudohyperparathyroidism:

- Paramalignant secretion of PTH – related peptide (PTH rP) from a ***malignant tumour***, (e.g. small cell bronchial carcinoma).
- Serum Ca: ↑, PTH: ↓.

CLINICAL PICTURE "Bones, Stones, Groans"

I. ASYMPTOMATIC.

II. SKELETAL MANIFESTATIONS

1. Bony pains.
2. Osteoporosis, pathological fractures.
3. Osteitis fibrosa cystica.

III. EXTRA-SKELETAL MANIFESTATIONS "Due to ↑↑ Ca"

1. RENAL:

- Polyuria: hypercalcemia makes the renal tubules less sensitive to ADH.
- Renal stones: bilateral, multiple, recurrent until correction of hypercalcemia.
- Renal calcification: *nephrocalcinosis* in the renal parenchyma & may end in **CRF**.

2. CARDIAC:

- Hypertension, bradycardia, arrhythmias, short QT interval on ECG.

3. NEUROLOGICAL:

- Neuropsychiatric disturbances: depression, apathy, DCL.
- Muscles: proximal muscle weakness.

4. GIT:

- Anorexia, nausea, vomiting, abdominal pain.
- PEPTIC ULCER.
- Constipation.
- PANCREATITIS.
- Gall stones.

5. EYE:

- Keratitis, conjunctivitis.

6. SKIN:

- Generalized itching.

7. METASTATIC CALCIFICATION:

- Chondro***calcinosis***.
- Nephro***calcinosis***.
- Calcification of the pancreas.
- Calcification of the arteries.

8. HYPERCALCEMIC CRISIS: (Acute hypercalcemia)

- It is a medical emergency with severe hypercalcemia > **14 mg / dL**, presenting with severe manifestations:

- GIT problems: *anorexia, nausea, vomiting, abdominal pain.*
- Renal problems: *polyuria & dehydration.*
- FEVER.
- Cardiac problems: *arrhythmias, cardiac arrest.*
- Neurological problems: *DCL, convulsions, coma, death.*

INVESTIGATIONS

A) CHEMISTRY

1. Blood chemistry:

- Calcium: ↑, Phosphate: ↓, Alkaline Phosphatase: ↑.

2. Urine analysis:

- Calcium: ↑, Phosphate: ↑, Volume: ↑.

B) HORMONES

1. Hormonal assay:

- PARATHORMONE: Elevated.

2. Steroid suppression test: "of limited use"

- *Normally*: Corticosteroids lower the serum Calcium by inhibiting vitamin D.
- *In disease*: Hydrocortisone 40 mg / 8 hours for 10 days will lower the serum Calcium in all causes of Hypercalcemia except in Hyperparathyroidism.

C) IMAGING

1. Imaging to localize the parathyroid tumour:

a) Ultrasonography, CT, MRI.

b) Radio-isotope subtraction scan:

- The neck is imaged during successive injections of 2 radioactive isotopes:
  - Thallium: is taken up BOTH by the *thyroid* & *parathyroid*.
  - Technetium: is taken up ONLY by the *thyroid*.
- Then image subtraction is done by the computer: → a parathyroid image.

2. Imaging for the clinical manifestations:

a) For the bone:

I. Plain X – ray:

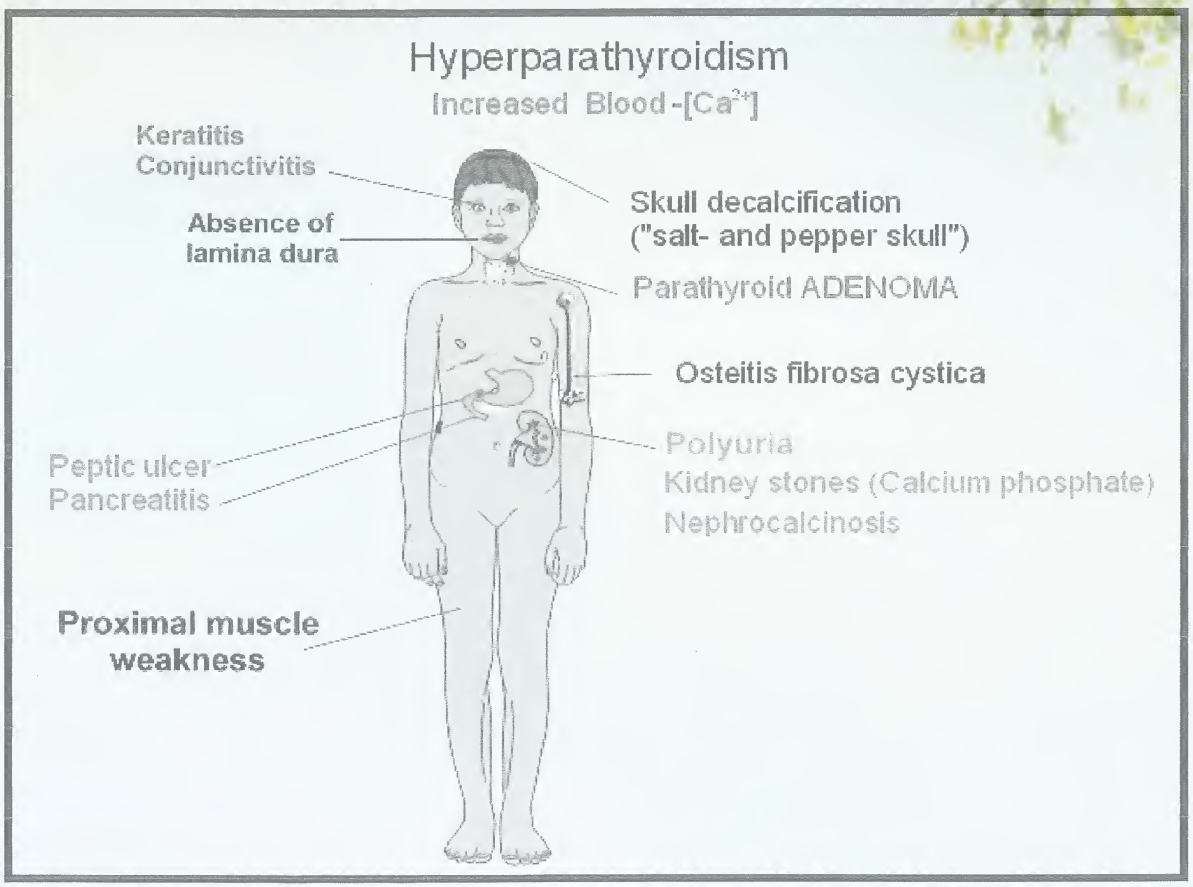
- **A**bsence of: the lamina dura around the teeth.
- **B**one cysts.
- **C**od-fish spine: indented vertebral bodies by intervertebral discs.
- **D**ecalcification: ground glass appearance of the bones.
- **E**rosion: sub-periosteal erosion of the phalanges.
- Salt & Pepper skull: mottling of the skull.

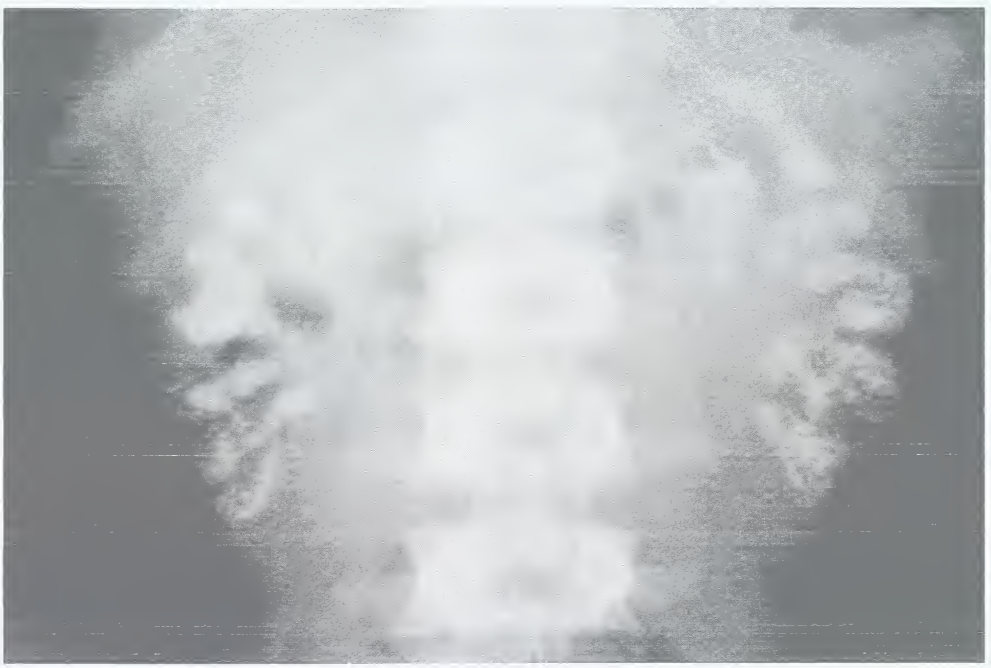
II. Bone Densimetry:

- Measure the bone mass by:
  Dual **E**nergy **X**-ray **A**bsorptiometry " **DEXA** ".
- It measures:
  the absorption of a beam of photons generated by an X-ray source to determine the BONE DENSITY.

b) For the urinary system: "PUT, IVP, Sonography"

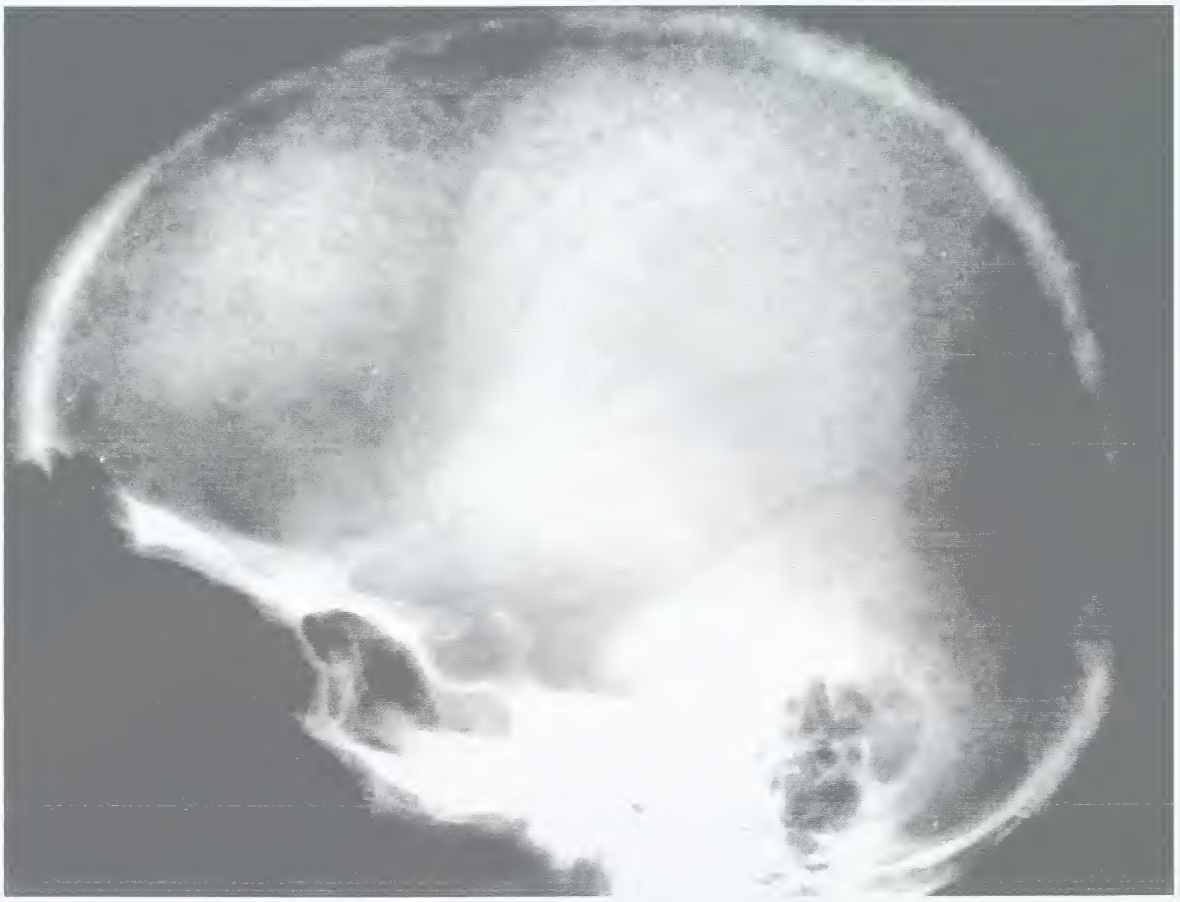
- Renal stones: bilateral, multiple.
- Renal calcification: *neprocalcinosis*.





Nephrocalcinosis

Bone cysts



Salt & Pepper skull

DD OF HYPERCALCEMIA

1. ENDOCRINAL

1. *Hyper*parathyroidism: *primary, tertiary, pseudohyperparathyroidism.*
2. *Hyper*thyroidism.
3. **A**ddison's disease.
4. **A**cromegaly.

} Reference *

2. IATROGENIC

1. Lithium.
2. Milk – alkali syndrome.
3. Excess calcium, Hypervitaminosis D, Hypervitaminosis A.
4. Diuretics: *Thiazides*.

3. MALIGNANCY

it causes hypercalcemia through:

1. ↑↑ osteoclastic activity: osteolytic metastasis, e.g. *MM*.
2. ↑↑ PTH rP secretion: paramalignant, e.g. *Bronchial carcinoma*.
3. Activation of Vitamin D: e.g. *Lymphoma*.
4. Prolonged immobilization: in terminal cases.

4. MISCELLANEOUS

1. Prolonged immobilization.
2. Sarcoidosis.
3. Paget's disease of the bone.
4. Familial hypocalcuric hypercalcemia:
   "A hereditary disease with ↑↑ tubular Ca reabsorption".

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* Differential diagnosis in Internal Medicine, Walter Siegenthaler, 2007, Ch 30, p. 936, table 30.28

TREATMENT

I. Surgical TTT:

- Surgical removal of the tumours.
- After surgery:
  - Calcium supplementation may be needed.
  - Complications include: *RLN paralysis*, *Hungry bone syndrome*.

II. Medical TTT:

A. TTT of the cause in secondary hyperparathyroidism.

B. Calcimimetic agents: Sensipar.

C. TTT of acute hypercalcemia: *"Hypercalcemic crisis"*

1. **Rehydration:**
   - IV saline: 5 liters are usually needed.
2. **Lowering the serum Calcium:**
   - **C**helation: Biphosphonates.
   - **C**alcitonin: 200 U / 6 hours IV.
   - **C**orticosteroids: Prednisone, 1 mg / Kg / day.
3. **Hemodialysis:**
   - May be needed in severe cases.

HYPOCALCEMIA

ETIOLOGY

1. HYPOPARATHYROIDISM:

A) Hereditary:

- Hypoplasia, or Absence (DiGeorge syndrome).
- Pseudohypoparathyroidism:
  - Endorgan resistance to PTH leading to: ↓ Ca, ↑ P, ↑ PTH.

B) Acquired:

- Iatrogenic: Surgical removal during thyroidectomy, neck irradiation.
- Immune: Isolated autoimmune destruction, or PGA – 1.
- Infiltrative: Hemochromatosis.
- Idiopathic.

2. pH & ELECTROLYTE IMBALANCE:

A) Alkalosis:

- *Total Calcium is kept constant BUT ionized fraction is ↓:*
  - Metabolic alkalosis.
  - Respiratory alkalosis.

} **Refer to "Nephrology"**

B) Hypomagnesemia:

- Decreased intake: Malnutrition.
- Decreased absorption: Malabsorption syndrome.
- Increased GIT loss: Severe vomiting & diarrhoea.
- Increased renal loss:
  - Diuretics: *Thiazides & frusemide.* ★
  - Osmotic diuresis: e.g. DM.
  - ATN: diuretic phase.
  - Alcoholism.

C) Hyperphosphatemia:

- Increased intake: ↑ parentral administration of phosphate.
- Decreased excretion: CRF, hypoparathyroidism.
- Tissue damage (*lysis*): hemo*lysis*, rhabdomyo*lysis*, tumour *lysis* syndrome.
- Endocrinal: acromegaly.

3. DECREASED INTAKE OF CALCIUM:

- Malnutrition.

4. DECREASED ABSORPTION OF CALCIUM:

- Malabsorption syndrome.

5. INCREASED EXCRETION OF CALCIUM:

- CRF.

6. INCREASED DEPOSITION OF CALCIUM:

- In the retroperitoneum: Acute pancreatitis.
- In the bones: Hungry bone syndrome.

7. DRUGS:

- **C**alcimimetic agents: Sensipar.
- **C**helating agents: Biphosphonates.
- **C**alcitonin.
- **C**orticosteroids.

8. HYPOALBUMINEMIA:

- *Ionized fraction is kept constant BUT Total Calcium is ↓:*
  - The patients do not have any symptoms or signs of hypocalcemia.
  - ↓ 1 gm/dL of serum albumin → ↓ 0.8 mg / dL of total calcium.
  - Corrected total calcium level is important..... ***How*** ??

CLINICAL PICTURE

1. CARDIAC:

- Hypotension, arrhythmias, long QT interval on ECG.
- Decreased myocardial contractility which may lead to HF.

2. SKIN:

- Skin: dry.
- Hair: loss.
- Nails: brittle.

3. NEUROLOGICAL:

- Neuropsychiatric disturbances: depression, irritability, dementia, DCL.
- SEIZURES.
- Neuromuscular: TETANY.

4. MISCELLANEOUS:

- Eye : cataract.
- Teeth: hypoplastic.

TETANY

DEFINITION

- Increased excitability of the ***nerve*** & ***muscle***.

MECHANISM

- *Hypocalcemia* * → disturbance in the membrane potential of the nerves. Therefore the neurons will depolarize too easily (↓ **neuronal threshold**). As a result, too many action potentials are sent to muscles causing spasms.

---

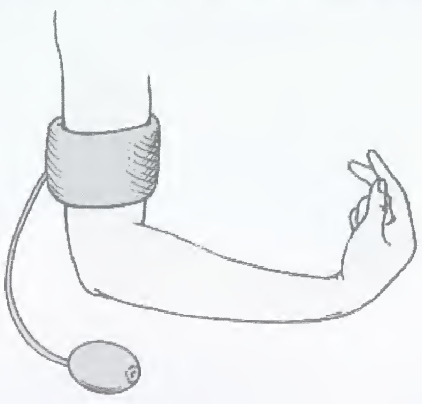
* The most common causes of tetany include: **Hypoparathyroidism, Alkalosis, ↓ Mg, ↑ P**

CLINICAL PICTURE

I. LATENT TETANY

- Manifestations of tetany *are absent*.
- Manifestations appear by *PROVOCATIVE TESTS*:

1. Erb's test:
   - Electric stimulation of nerves by less than 4 milli-amperes → muscle contraction, (normally: 8 milli-amperes at least are needed for stimulation).
2. Chvostek's sign: *
   - Tapping of the facial nerve in front of the ear → *contraction of the facial muscles*: The response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of hypocalcemia.
3. Trousseau's sign: *
   - Inflating the sphygmomanometer above SBP for 3 minutes → spasm of the muscles of: *the hand & the forearm*.



Trousseau's sign

* It was first described by František Chvostek (1835 – 1884), a Czecho-Austrian physician.

* It was first described by Armand Trousseau (1801 – 1867), a French physician.

II. MANIFEST TETANY

- Manifestations of tetany *are present:*

1. **NERVES:**
   - Parasthesia: numbness & tingling in perioral area, fingers, toes.

2. **MUSCLES:** "Muscle twitches or Muscle spasms"
   - Muscle spasms:
     - Eye lids → Blepharospasm.
     - Laryngeal muscles → laryngismus stridulus.
     - Facial & masseter muscles → risus sardonicus & trismus.
     - *CARPOPEDAL SPASM.*
     - Diaphragm → hiccough.
     - GIT → abdominal colics.

INVESTIGATIONS "of the cause of Hypocalcemia"

1. **In Hypoparathyroidism:**
   - Serum *Calcium*: ↓, serum **PTH**: ↓, serum *Phosphate*: ↑.

2. **In Alkalosis:**
   - Serum *Calcium*: N, serum **PTH**: N, serum *Phosphate*: N.
   - Serum ionized Calcium: ↓ pH: ↑.

3. **In Hypomagnesemia:**
   - Serum *Calcium*: ↓, serum Magnesium: ↓.

4. **In Hyperphosphatemia:**
   - Serum *Calcium*: ↓, serum Phosphate: ↑.

TREATMENT

A) Treatment of the attack:

- IV Ca gluconate: 10 ml of 10 % solution over 10 minutes (very slowly IV).

B) Treatment in between the attacks:

1. Calcium supplementation:

- Ca gluconate: 1 – 3 mg / day orally.
- Vitamin D preparations:
  - Vitamin D3 (cholecalciferol): 50,000 U / day orally.
  - Dihydrotachysterol (AT 10): 0.5 mg / day orally.

2. TTT of the cause of hypocalcemia: e.g.

- Alkalosis: refer to "Nephrology".
- ↓ Mg: ttt of the cause + Mg supplementation
- ↑ P: ttt of the cause + dietary restriction + P binders.

CUSHING'S SYNDROME *

DEFINITION

- It is a clinical state resulting from: INCREASED GLUCOCORTICOIDS.

ETIOLOGY

A. EXOGENOUS ADMINISTRATION "IATROGENIC"

"The more common cause"

- It is called: **Cushingoid syndrome** and it is due to either:
  1. Prolonged administration of cortisol: common.
  2. Prolonged administration of ACTH: less common.

B. ENDOGENOUS OVERPRODUCTION "DISEASE"

"The less common cause"

I. Excess ACTH secretion: "ACTH – DEPENDENT"

1. Excess Pituitary *ACTH secretion:* = **CUSHING'S DISEASE**
   - It occurs in pituitary tumours **(pituitary adenoma)**.
   - It represents **70 %** of the spontaneous type.
2. Ectopic *ACTH secretion:*
   - It occurs in paramalignant syndrome **(e.g. small cell br. carcinoma)**.
   - It represents **15 %** of the spontaneous type.

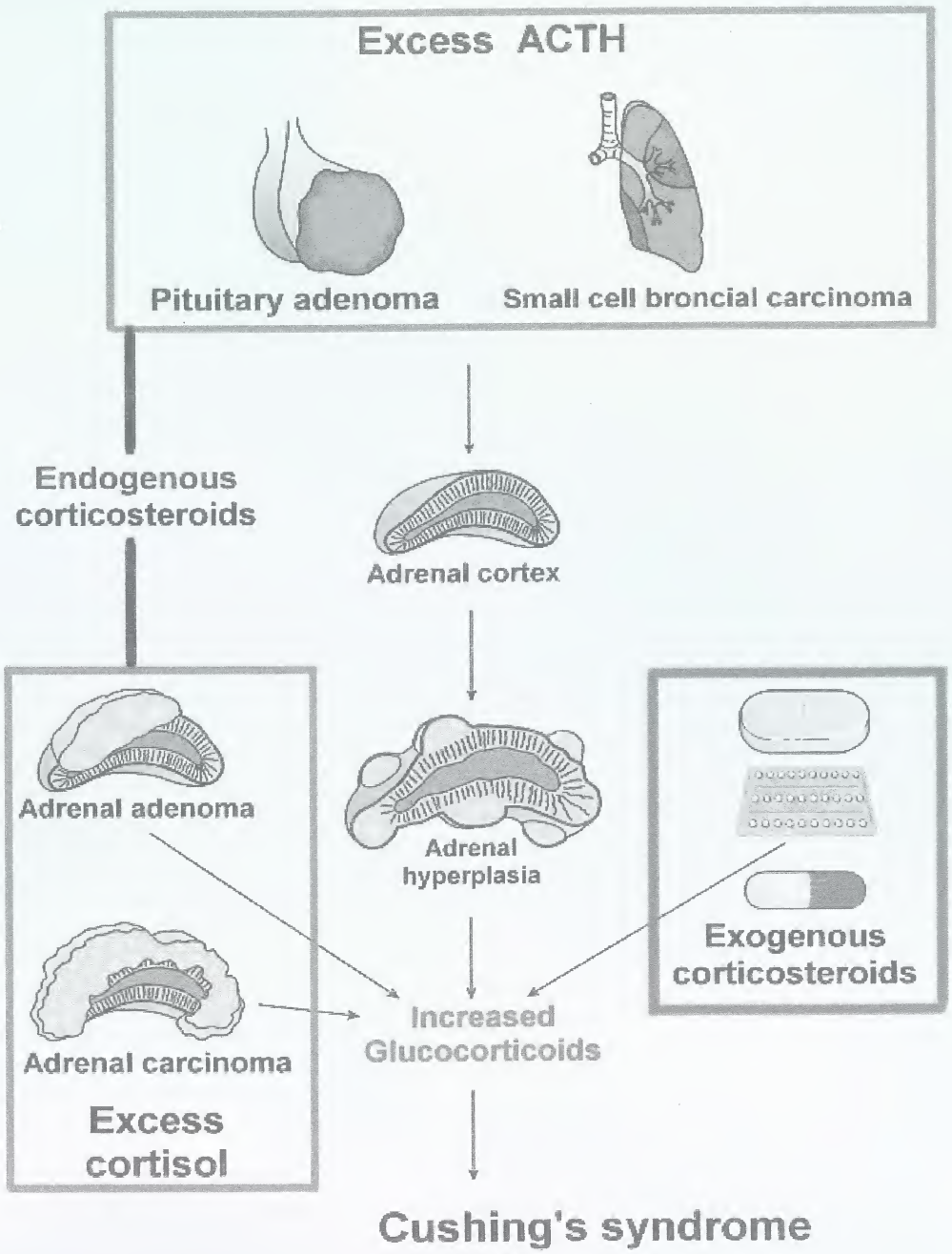
II. Excess cortisol secretion: "ACTH – INDEPENDENT"

- It occurs in primary adrenal tumours **(adenoma or adenocarcinoma)**.
- It represents **15 %** of the spontaneous type.

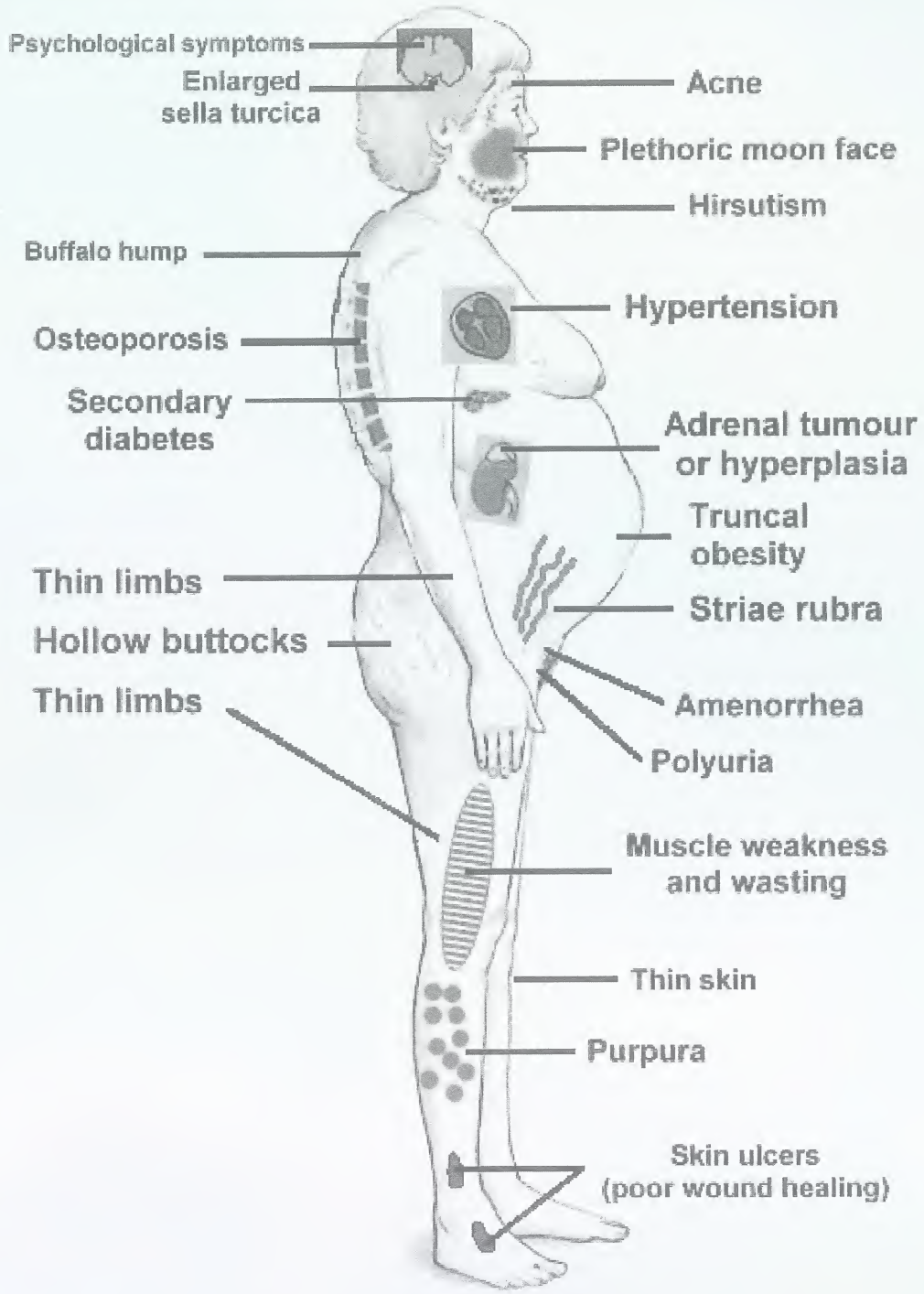
---

* It was first described by Harvey Cushing (1869 – 1939), an American neurosurgeon

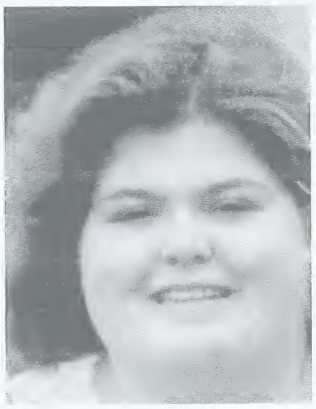
Etiology of Cushing's syndrome

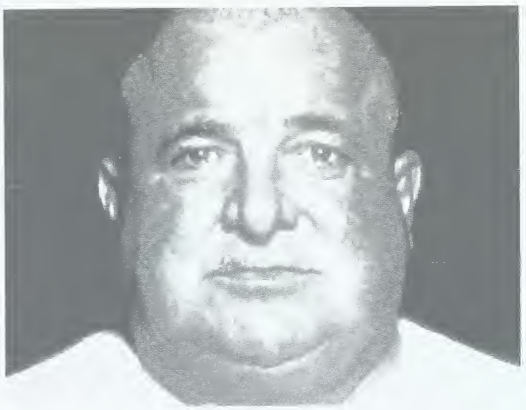


Clinical picture of Cushing's syndrome

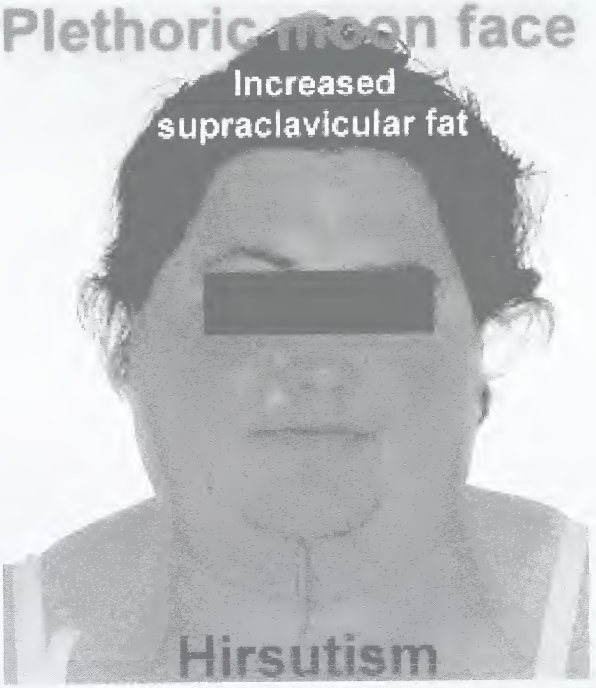


Moon face

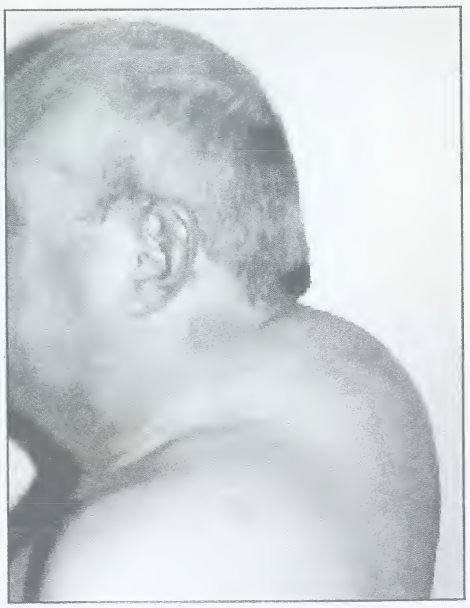


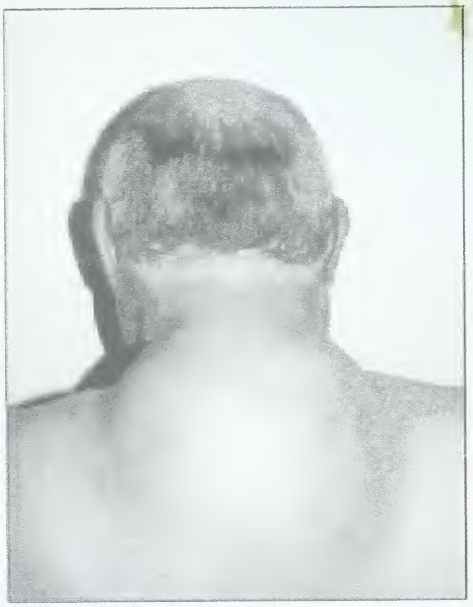


Plethoric moon face



Buffalo hump

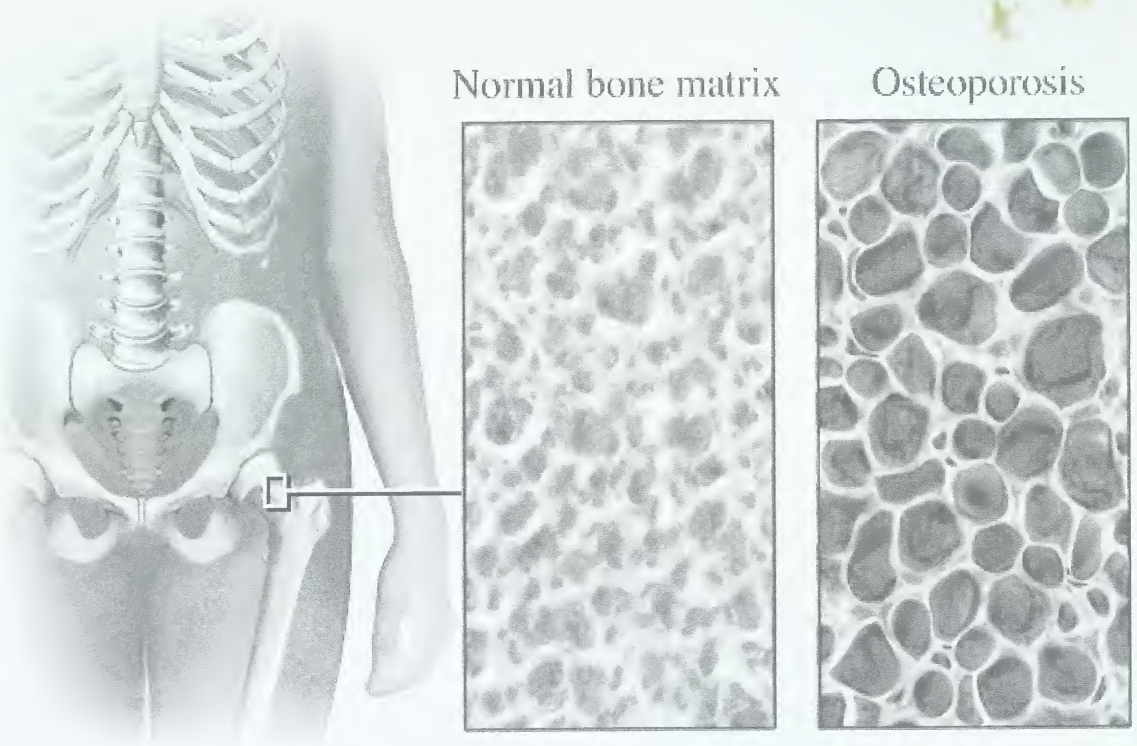


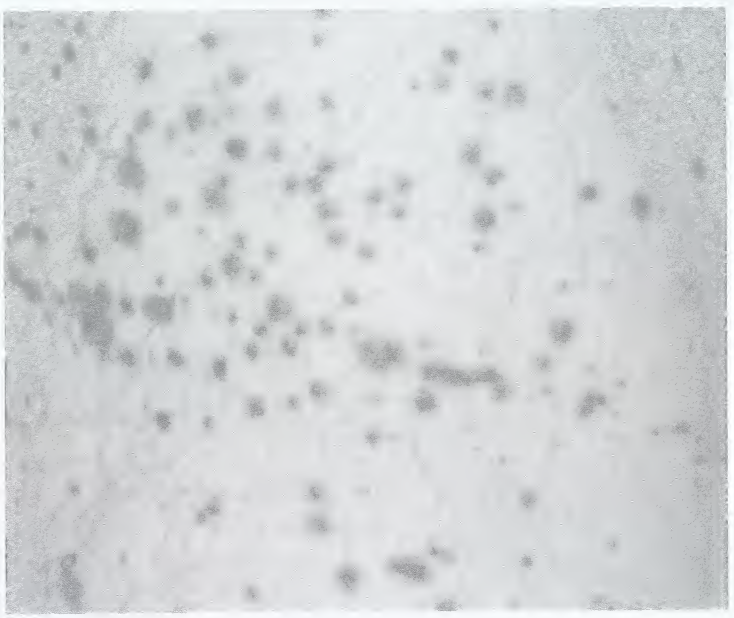


Truncal (central) obesity

Red striae

Osteoporosis





Purpura

CLINICAL PICTURE

- INCIDENCE: *Age: 30 – 40 years,* *Sex: more common in ♀.*

1. Disturbances in Fat metabolism:

- *Moon-face:* rounded face with bloated cheeks.
- *Buffalo hump:* ↑ fat in the interscapular & supraclavicular region.
- *Truncal obesity:* central obesity,
  - Increased fat in breasts & abdominal wall.
  - Hollow buttocks & thin limbs.

2. Disturbances in Protein metabolism:

- Muscles: wasting, weakness, myopathy.
- Bones: osteoporosis *(bony pain, kyphosis, pathological fractures)*.
- Skin:
  - Thin skin.
  - Skin ulcers (poor healing of wounds).
  - Vascular purpura, bruises (↓ support of the blood vessels).
  - Skin infections (especially fungal & bacterial).
  - STRIAE: *(over the breasts, abdomen, buttocks, upper thighs, upper arms)*

    1. *Striae rubra (red):*

       Red or purple lines appear due to rupture of the weak SC collagen fibres → exposure of the vascular SC tissue.

    2. *Striae alba (white):*

       White lines due to prolonged skin stretch.

3. Disturbances in CHO metabolism:

- Hyperglycemia:

  Impaired glucose tolerance → Secondary Diabetes (Steroid Diabetes).

4. Disturbances in Fluid & Electrolytes:

- Sodium: retention → Secondary Hypertension.
- Potassium: loss → hypokalemia & polyuria (K diuresis).
- pH: alkalosis → tetany.

5. Other manifestations:

- **P**sychological symptoms: *depression* or *psychosis*.
- **P**olycythemia: plethoric face.
- **P**igmentation of the skin: *in cases of excess ACTH secretion*.
- Peptic ulcer
- **I**nfections: especially skin infections (fungal & bacterial).
- **I**mpaired growth: growth retardation occurs in children.
- **I**mpaired gonadal function:
  - **Female**: amenorrhea, hirsutism, acne,
  - **Male**: ↓ libido, impotence, acne.

INVESTIGATIONS

I. To diagnose Cushing's syndrome:

1. Cortisol level in plasma:

- Normally: 5 – 20 ug / dL, with normal circadian rhythm (lowest at midnight).
- In Cushing's: **early**: loss of circadian rhythm, **late**: persistent cortisol elevation.

2. Cortisol level in urine:

- Elevated urinary free cortisol (in a 24 – hour urine specimen). 17-Keto steroid

3. Blood chemistry:

- Glucose: ↑.
- Sodium: ↑.
- Potassium: ↓.
- pH: ↑.

4. Blood picture:

- RBCs: ↑.
- WBCs: ↑ *neutrophils,* ↓ *lymphocytes, eosinophils, basophils.*

5. Dexamethazone suppression test "low dose":

- **Method:**
  - Dexamethazone (synthetic glucocorticoid) is given in a **low dose**: (0.5 mg /6 h for 2 days).
- **Result:**
  - *Normally:*

    Cortisol level in blood & urine is suppressed, *because,*
    Dexamethazone will inhibit ACTH by: – ve feedback.
  - *In Cushing's syndrome:*

    Cortisol level in blood & urine is not suppressed, *because,*
    There is pathological secretion of either ACTH or cortisol.

II. To diagnose the cause:

1. Plasma ACTH:

- **Low:** in primary adrenal tumours (inhibition of ACTH by – ve feedback).
- **High:** in pituitary tumours secreting excess ACTH.
- **Very high:** in ectopic tumours (e.g. br. carcinoma) secreting much excess ACTH.

2. Dexamethazone suppression test "High dose":

- **Method:**
  - Dexamethazone (synthetic glucocorticoid) is given in a **high dose**: (2 mg / 6 h for 2 days).
- **Result:**
  - *In pituitary tumour:*

    Cortisol level in blood & urine is suppressed.
  - *In adrenal & ectopic tumours:*

    Cortisol level in blood & urine is not suppressed.

3. Imaging:

- **Adrenal tumours:** CT scan, MRI, Abdominal ultrasonography.
- **Pituitary tumours:** CT scan, MRI.
- **Bronchial carcinoma:** CT scan, MRI.

DIFFERENTIAL DIAGNOSIS

1. From other causes of obesity.
2. From other causes of osteoporosis.
3. From other causes of polyuria.
4. From other causes of hirsutism.
5. *From other causes of* ***secondary hypertension***.
6. *From other causes of* ***secondary diabetes***.
7. DD of the cause (Scheme……)…….. **VIP**.

- **Important question:** **"Self – assessment"**

"Differentiate the 2 ACTH dependent causes of Cushing's syndrome".

Do not forget:

- Petrosal Sinus Sampling (PSS).
- Corticotropin Releasing Hormone test (CRH).

TREATMENT

Metyrapone / Ketoconazole → Anti-fungal
↓ Cortisol 1500 mg / 7 days → damage to Supra-renal

1. Adrenal tumours:

- Surgical removal of the tumour followed by suboptimal replacement therapy (low dose corticosteroids) for several months till the other atrophic gland recovers from suppression.

2. Pituitary tumours: "*Cushing's disease*"

- Surgical removal *or* irradiation of the tumour, followed by replacement therapy.
- Nelson's syndrome:

  TTT of pituitary Cushing's disease by bilateral adrenalectomy may lead to the development of a locally invasive pituitary tumour with very high levels of ACTH & Hyperpigmentation.

Yettrium 90

3. Bronchial carcinoma: " *Paramalignant syndrome* "

- TTT of the primary tumour, if possible.

ADDISON'S DISEASE *
(CHRONIC ADRENAL FAILURE)

ETIOLOGY

I. PRIMARY ADRENAL FAILURE (Addison's disease)

- **The problem is in the adrenal glands:** ↓ Cortisol, Aldosterone, sex

  - **I**mmune: Autoimmune disease is the most common cause (80 %).
  - **I**nfection: TB, HIV, CMV, Fungal.
  - **B**ilateral: adrenalectomy.
  - **B**ilateral: adrenal hemorrhage or infarction.
  - **M**alignancy: Metastases esp. from bronchial carcinoma, Lymphoma.
  - **M**etabolic: Amyloidosis, Hemochromatosis., Sarcoidosis
  - *Congenital:* *Hypoplasia & Hyporesponsiveness to ACTH.*

II. SECONDARY ADRENAL FAILURE Panhypopituitarism

- **The problem is not in the adrenal gland itself; the problem is supra-adrenal:**

  1. *Pituitary dysfunction.*
  2. *Hypothalamic dysfunction.*

↓ Cortisol, sex hormones
Not aldosterone

CLINICAL PICTURE

- **It results from:**

  - Mainly: Decreased Glucocorticoids.
  - Maybe: Decreased Mineralocorticoids & Androgen.
  - Maybe: Increased ACTH.

---

* It was first described by Thomas addison (1793 – 1860), a British physician

1. ASTHENIA (marked weakness, fatigue & weight loss) Due to:

- ↓ cortisol & aldosterone → ↑ K → muscle flaccidity.
- ↓ cortisol & aldosterone → ↓ Na → hypotension.
- ↓ cortisol → ↓ glucose → brain energy & drowsiness.
- ↓ androgen → muscle weakness.

2. HYPOTENSION

- ↓ cortisol & aldosterone → ↓ Na → hypotension.
- POSTURAL HYPOTENSION IS CHARACTERISTIC.
  - **Important questions:** **"Self – assessment"**
    - Why does Hyponatremia cause Hypotension ??
    - What should you do during measuring BP ??
    - When is Hypotension more severe, in *primary* or in *secondary* adrenal failure ??

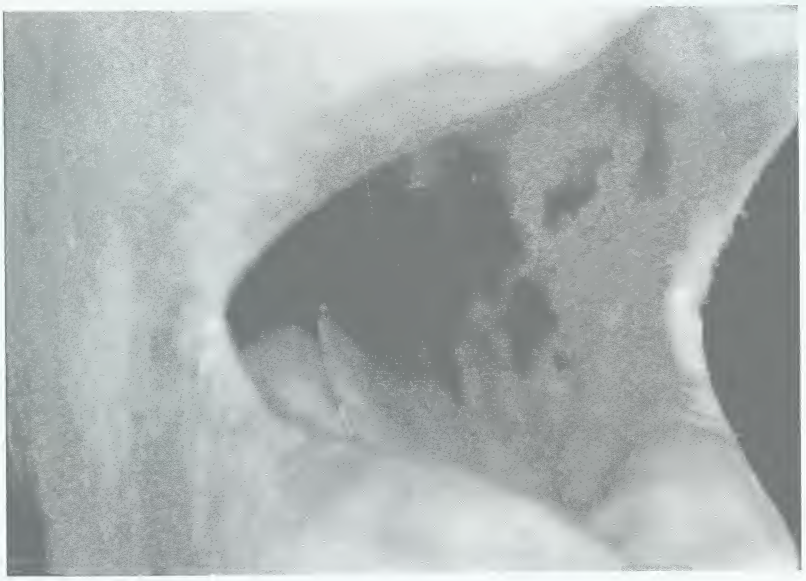
3. HYPOGLYCEMIA

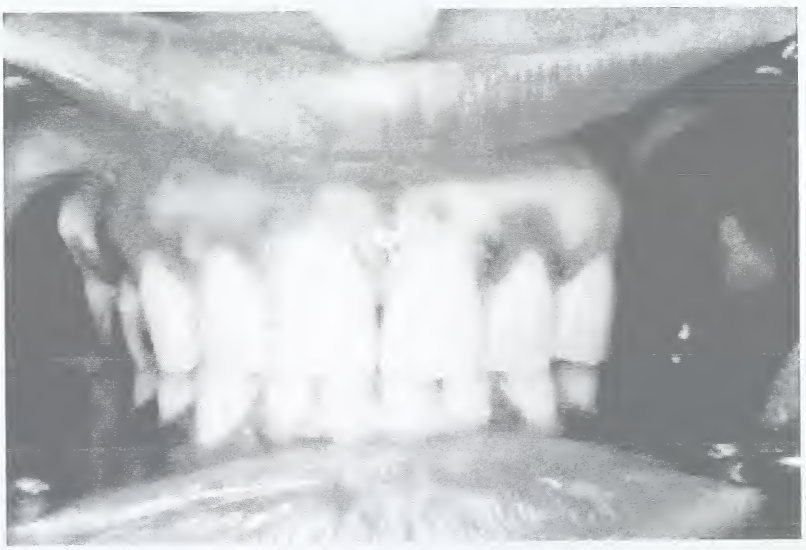
- Manifestations: "Refer to Hypoglycemia".
- Maybe: there will be absence of the warning manifestations of hypoglycemia due to decreased catecholamines ….. ***why*** ??
- ***What happens if Addison's disease occurs in a diabetic patient ??***

4. HYPERPIGMENTATION

- It is due to: high level of ACTH.
- It occurs in: primary and not in secondary adrenal failure.
- It affects:
  - skin: skin creases, scars, normally pigmented areas as nipples.
  - mm: buccal mucosa, gums, tongue, (remember **Peutz-Jeghers** Syndrome).
- It may be associated with:
  - Vitiligo in 10 % of the cases (autoimmune affection).

Hyperpigmentation in Addison's disease (mm)





5. GIT MANIFESTATIONS

- Anorexia, nausea & vomiting.
- Abdominal pain.
- DIARRHEA.

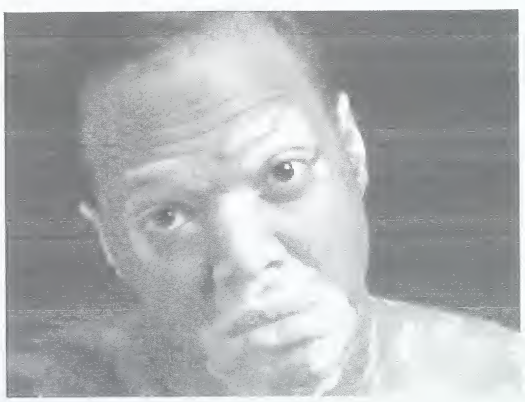
6. OTHER MANIFESTATIONS

- ***Genital:***
  - ♂: ↓ body hair, ↓ libido, Impotence.
  - ♀: Amenorrhea.
- ***Urinary:***
  - Polyuria: *due to Na diuresis*.
- ***Disturbances in Fluid & Electrolytes:***
  - Sodium: ↓ → Hypotension, especially postural.
  - Potassium: ↑ → muscle flaccidity.
  - pH: acidosis.
- ***Associated autoimmune diseases:***
  - PA.
  - Hashimoto's thyroiditis: *causing myxoedema*.
  - Vitiligo.

7. ADDISONIAN CRISIS

- See later.

Vitiligo (Irregular white patches)



INVESTIGATIONS

I. To diagnose Adrenal failure:

1. Cortisol level in plasma:

- Decreased.

2. Cortisol level in urine:

- Decreased.

3. Blood chemistry:

- Glucose: ↓.
- Sodium: ↓.
- Potassium: ↑.
- pH: ↓.
- Calcium: ↑.? due↓ Anti-vit D action of Cortisol "Over active Vit. D"

4. Blood picture:

- RBCs: ↓. anemia
- WBCs: ↓ *neutrophils,* ↑ *lymphocytes, eosinophils, basophils.*

II. To diagnose the cause:

1. Plasma ACTH:

- **High:** in primary adrenal failure (Addison's disease).
- **Low:** in secondary adrenal failure.

2. ACTH stimulation test:

- **Method:**
  - Synacthen (synthetic ACTH) is given IM or IV & plasma cortisol levels are estimated.
- **Result:**
  - *In primary adrenal failure (Addison's disease):*
    Cortisol level in blood is not increased.
  - *In secondary adrenal failure:*
    Cortisol level in blood is increased.

3. Serology:

- Detection of adrenal antibodies in autoimmune cases.

4. Imaging:

- Abdominal sonar, X-ray, CT, MRI: Adrenal calcifications in TB.
- CXR: TB lesions.

DIFFERENTIAL DIAGNOSIS

1. From other causes of asthenia.
2. From other causes of hypercalcemia.
3. From other causes of polyuria.
4. From other causes of diarrhea.
5. *From other causes of **postural hypotension**.*
6. *From other causes of **hypoglycemia**.*
7. From other causes of skin pigmentation:
   a) *Addison's disease.*
   b) *Pituitary Cushing's disease.*
   c) *Pregnancy.*
   d) *Pellagra.*
   e) *Primary biliary cirrhosis.*
   f) *Hemochromatosis.*
   g) *Neurofibromatosis.*
   h) *Leprosy.*
   i) *DM.*
   j) *Skin diseases.*
8. Differentiation between **primary** & **secondary** adrenal failure:
   ..... **How ??**

TREATMENT

1. **Replacement therapy:**
   - Oral cortisol (glucocorticoid):
     1mg / Kg / day, to be increased in stressful conditions.
   - Flurohydrocortisone: (mineralocorticoid): Fluoro-nil
     0.1 mg / day to replace aldosterone, especially if hypotension is persistent.
2. **TTT of the cause:**
   - e.g. Anti – TB drugs for TB.
3. **TTT of Addisonian crisis:**
   - See later.

ADDISONIAN CRISIS
(ACUTE ADRENAL FAILURE)

ETIOLOGY

1. Addison's disease: **if** subjected to severe *stress, infections, trauma, surgery.*
2. Simmond's disease: **if** ttt is initiated with thyroxin without cortisol.
3. **W**aterhouse – Friderichsen syndrome: " refer to neurology ". Meningococcal Septicaemia
4. **W**ithdrawal of chronic corticosteroid therapy **SUDDENLY** after prolonged ttt. ↓ DIC ↓
5. Bilateral adrenalectomy without adequate corticosteroid replacement.

CLINICAL PICTURE

1. Sudden onset of: ***severe weakness, mental confusion, anorexia, N, V, abdominal pain, & diarrhea.***
2. Dehydration & Shock. hypotension ↓ Na+ , hypovolaemia
3. If not treated urgently, coma & later death may occur.

INVESTIGATIONS

1. **Cortisol level in plasma:**
   - Decreased.
2. **Blood chemistry:**
   - Glucose: ↓, Na: ↓, K: ↑, pH: ↓.

TREATMENT

"Medical emergency"

1. **Aggressive IV fluid replacement:** hypovolaemic
   - NaCl (0.9 %): normal saline.
   - Glucose (10 %). 1-5 L
2. **Hydrocortisone IV:** the same dose as status asthmaticus
   - 200 mg IV, then 100 mg IV every 6 h till GIT manifestations stop, then shift to oral cortisol. Emergency ended, He can accept oral
3. **Other anti – shock measures.,** e.g. pressors (as dopamine).
4. **TTT of the precipitating factors,** e.g. proper control of infection.

DOCA IM

List of famous Addisonians

- **John F. Kennedy** (United States President)

- **Helen Reddy** (Popular singer)

DIABETES INSIPIDUS

DEFINITION

- A disease characterized by production of ***abnormal urine***:
  - Large volume (POLYURIA).
  - Diluted.
- It is due to:
  - Decreased secretion of ADH (Central, Cranial DI).
  - Decreased action of ADH (Nephrogenic DI).

ETIOLOGY

I. Decreased secretion of ADH "Central, Cranial DI"

A) **Disease of: HYPOTHALAMUS or POST. PITUITARY**

- Congenital: *pituitary malformation.*
- Inflammatory: *meningitis, encephalitis.*
- Traumatic: *head trauma.*
- Neoplastic: *pituitary tumours.*
- Infiltrations: *sarcoidosis.*
- Iatrogenic: *post – surgical, pituitary irradiation.*
- Idiopathic.

B) **Disease of: OSMORECEPTORS**

- Hereditary defect in the osmoreceptors of the hypothalamus making them insensitive to changes in the osmotic pressure of the plasma.
- This disease is also called: *essential hypernatremia.*

II. Decreased action of ADH "Nephrogenic DI"

- There is lack of response of the renal tubules to the action of ADH:
  - Hereditary.
  - Acquired: ↑ *Ca,* ↓ *K,* drugs, e.g. *Lithium, Amphotericin B.*

CLINICAL PICTURE

1. **Polyuria:**
   - Marked **Polyuria** by day & night (3 – 20 litres / day).
   - Marked **Thirst** sensation & **polydipsia**.

2. **Dehydration:**
   - Features of dehydration: may occur.

3. **Complications:**
   - Hypovolemia: Hypovolemic shock & maybe ARF.
   - Hypernatremia: Hypertonic encephalopathy *(DCL, convulsions, coma)*.

4. **Features of the cause:** e.g. *pressure manifestations of a pituitary tumour*.

DD OF POLYURIA

1. **Renal causes:**
   - Chronic renal failure.
   - Diuretic phase of acute renal failure.
   - Nephrogenic DI.
   - Renal tubular disorders.

2. **Endocrinal causes:**
   - Diabetes insipidus.
   - Diabetes mellitus.
   - Hyperparathyroidism & Hypercalcemia.
   - Cushing's syndrome, Addison's disease, Conn's syndrome.

3. **Functional causes:**
   - Exposure to cold weather.
   - Excessive intake of: *fluids, coffee, tea.*

4. **Hysterical polydipsia:**
   - Water deprivation test.

INVESTIGATIONS

A. TO DIAGNOSE DI

Urine analysis: (To confirm DI)

- Volume: 3 – 20 litres / day.
- Specific gravity: Low (1001 – 1004) & fails to ↑ with fluid restriction.

Water deprivation test: (To differentiate DI from hysterical polydipsia)

- DI: urine volume remains ↑ & specific gravity remains ↓.
- Hysterical polydipsia: urine volume ↓ & specific gravity ↑.

B. TO DIAGNOSE THE CAUSE OF DI

1. **Estimation of plasm ADH:**
   - Central DI: Low level.
   - Nephrogenic DI: Normal or high level.
2. **Vasopressin test (IV):**
   - Central DI: Positive response (urine volume ↓).
   - Nephrogenic DI: No response.
3. **Brain imaging:** (MRI)
   - Central DI: a pituitary tumour may appear.
   - Nephrogenic DI: normal brain imaging.

TREATMENT

1. **Central DI:**
   - Synthetic vasopressin (Desmopressin nasal spray, 20 µg / day).
2. **Nephrogenic DI:**
   - Thiazides, chlorpropamide, NSAIDs *(may be beneficial in some cases)*.
3. **Adequate fluid intake.**
4. **TTT of the cause if possible.**

HIRSUTISM

DEFINITION

- Excessive growth of body hair in females.

ETIOLOGY

A. HIRSUTISM WITHOUT VIRILIZATION:

1. Idiopathic: *the most common cause.*
2. Iatrogenic: minoxidil, androgens, cyclosporin.
3. Familial & Racial.
4. Polycystic ovary: mild cases.

B. HIRSUTISM WITH VIRILIZATION:

1. Congenital adrenal hyperplasia.
2. Adrenal tumours.
3. Ovarian tumours.
4. Polycystic ovary: severe cases.

GYNECOMASTIA

DEFINITION

- Enlargement of the male breast due to hypertrophy of the glandular tissue.

ETIOLOGY

" Decreased androgen / estrogen ratio "

1. **Physiological:**
   - Neonatal (↑ estrogen), pubertal (↑ estrogen), old age (↓ androgen).
2. **Pathological:**
   a) Endocrinal: Hypogonadism, Hypothyroidism, Hypothyroidism.
   b) Metabolic: Chronic renal *failure* Liver cell *failure*.
   c) Malignant: Estrogen-producing tumours of the testis or adrenals.
3. **Iatrogenic:**
   - Estrogen, Digitalis, Spironolactone, Cimetidine.
4. **Idiopathic.**

HYPOGLYCEMIA

ETIOLOGY

1. **Endocrinal:**
   - Hypopituitarism.
   - Addison's disease.
   - Hyperinsulinemia: *overdose of insulin, insulinoma, paramalignant, CRF.*

2. **Non – Endocrinal:**
   - Decreased glucose intake: starvation.
   - Decreased glucose absorption: malabsorption.
   - Increased demand: heavy exercise & pregnancy.
   - Increased loss: renal glycosuria.
   - ACUTE LIVER FAILURE.

CLINICAL PICTURE

1. **Insufficient glucose to the brain leading to:**
   - Lack of concentration, mental dullness, hallucinations, convulsions, coma.

2. **Manifestations of sympathetic overcativity due to hyperadrenalism:**
   - Irritability, tremors, pallor, sweating, palpitation (tachycardia).

INVESTIGATIONS

1. Blood: markedly low blood glucose (less than 50 mg / dL).
2. Urine: no glucose in urine.
3. Investigations for the cause.
4. C – peptide.

TREATMENT

1. TTT of the cause.
2. TTT of hypoglycemic coma: " refer to DM".

OBESITY

DEFINITION

- A state of excess ADIPOSE tissue mass.

ETIOLOGY

I. IDIOPATHIC (95 %)

1. Familial: genetically determined factors or same pattern of eating.
2. Excessive caloric intake: excessive intake of fats or carbohydrates.
3. Diminished caloric consumption: physical inactivity.

II. SECONDARY

1. Endocrinal: *Cushing's syndrome, Myxoedema, Hypogonadism, Insulinoma, Pregnancy.*
2. Hypothalamic disturbances: *Diabetes insipidus, polyphagia, obesity, hypersomnia.*
3. Drugs: they stimulate the appetite, e.g. *insulin, CCPs, corticosteroids.*

MEASUREMENT

1. **Body Mass Index** (BMI) = Weight / Height ^{2} (Average: 18 – 25).
   Mild (BMI = 27 – 30), Moderate (BMI = 30 – 40), Marked (BMI > 40).
2. **Anthropometry:** measure the skin fold thickness, e.g. *over the Triceps.*

DISTRIBUTION OF BODY FAT

- Measure the: WAIST / HIP ratio:

1. **Male (Android) pattern:**
   - More fat in the upper body (associated with more morbidity & mortality).
2. **Female (Gynecoid) pattern:**
   - More fat in the lower body (associated with less morbidity & mortality).

COMPLICATIONS

1. METABOLIC SYNDROME:
   - Refer to " DM ".

2. CARDIOVASCULAR:
   - Coronary artery disease.
   - Hypertension.
   - Hyperlipidemia & Atherosclerosis.
   - DVT & Varicose veins.

3. RESPIRATORY:
   - Restrictive hypoventilation & Pickwickian syndrome.
   - Sleep apnea syndrome.

4. GIT:
   - Cholesterol gall stones & cholecystitis.
   - GORD & Hiatus hernia.
   - Fatty liver.

5. NEUROLOGICAL:
   - Cerebrovascular Stroke.
   - Carpal tunnel syndrome.

6. JOINTS:
   - Osteoarthrosis.
   - Back pain.
   - Increased incidence of gout.

7. MALIGNANCY:
   - Increased incidence of: cancer colon, rectum, GB, breast.

8. PSYCHOLOGICAL:
   - Depression, Anxiety.

TREATMENT

1. **Reduction in caloric intake:** **" Diet ttt "**
   - The aim is to lose 1 kg / week.

2. **Increase in caloric loss:** **" Exercise "**
   - It should be encouraged, BUT: *exercise alone is not enough to lose weight.*

3. **Drugs:**
   a) Anorexic drugs: e.g. fenfluramine.
   b) Orlistat: inhibits the pancreatic lipase & so ↓ fat absorption.

4. **Surgery:**
   a) Jejuno-ileal bypass: causes malabsorption (not used now).
   b) Gastric balloon: a balloon is placed endoscopically in the stomach & inflated.
   c) Gastric plication: stapling across the stomach will produce a small gastric pouch.

OSTEOPOROSIS

DEFINITION

Reduction in the BONE MASS leading to:

- Increased bone fragility.
- Increased risk of fracture.

ETIOLOGY

1. POST-MENOPAUSAL (Type I).
2. OLD AGE (Type II).

3. Endocrinal: *Cushing's syndrome, Hypogonadism Hyperthyroidism, Hyperparathyroidism.*
4. Failure: *Renal failure, Liver failure, failure of absorption (MALABSORPTION).*
5. Malignancy: *Multiple myeloma, terminal malignancy.*
6. Iatrogenic: *Corticosteroids, long term heparin, long term diuretics.*
7. Inherited: *Osteogenesis imperfecta.*
8. Immobilization.
9. Idiopathic.

CLINICAL PICTURE

1. EARLY:
   - Asymptomatic.
2. LATE:
   - Bone pains & Bone tenderness.
   - Pathological fractures & Deformities.

INVESTIGATIONS

1. Plain X-ray:

- Decreased bone density (osteopenia).
- Deformities, fractures, vertebral collapse.

2. Bone Densimetry:

- Measure the bone mass by: **D**ual **E**nergy **X**-ray **A**bsorptiometry " **DEXA** ".
- It measures: the absorption of a beam of photons generated by an X-ray source to determine the BONE DENSITY.

TREATMENT

1. GENERAL MEASURES:

- Diet: adequate *Proteins*, *Calcium*, *Vitamin D*.
- Calcium carbonate orally.
- Vitamin D orally.

2. HORMONE REPLACEMENT THERAPY (HRT):

- Estrogen therapy: especially in *premature menopause*, *ovariectomy*, *hypogonadism*.
- Androgen therapy: should be given to hypogonadal men.

3. BIPHOSPHONATES:

- They inhibit bone resorption.

4. CALCITONIN.

5. TTT of the cause: e.g. *Cushing's syndrome*.

PHEOCHROMOCYTOMA

DEFINITION

- Tumours that secrete CATECHOLAMINES.
- 90 % arise in the ADRENAL MEDULLA, *others in the sympathetic chain in abdomen.*
- 90 % are UNILATERAL.
- 90 % are BENIGN.
- 90% are Single

CLINICAL PICTURE

1. GENERAL: **the commonest symptoms are** ATTACKS **of:** ***headache, sweating, pallor, palpitation, tremors.***
2. HYPERTENSION: secondary & paroxysmal.
3. DIABETES: secondary.
4. HYPERTROPHIC CARDIOMYOPATHY.

Associations !!

INVESTIGATIONS

- Clonidine : not used nowadays
test

1. INCREASED CATECHOLAMINES:
   - In plasma & in urine.
     immediately because of rapid break down, neurophysin is better
2. INCREASED URINARY VMA.
   ↳ Vanylyl mandelic acid
   - 24 hrs urine to get average results
   لا تأكل الموز والباذنجان
3. IMAGING:
   - CT, MRI: of the abdomen. α, methyl dopa & Tyramine
   - **MIBG:** scanning with **M**eta **I**odo **B**enzyl **G**uanidine produces specific uptake in sites of ***sympathetic activity***.

TREATMENT

1. Surgical: removal of the tumour is the ttt of choice if possible.
2. Medical: combined alpha (ألفا) & ßeta adrenergic blockers: ⇐ β blockers
   - *For pre- & post- operative ttt.*
   - *If surgery is not possible.*

كعلاج للضغط على المريض

PRIMARY HYPERALDOSTERONISM
" CONN"S SYNDROME "

ETIOLOGY

1. Adrenal adenoma: the most common cause.
2. Adrenal hyperplasia: bilaterally.

CLINICAL PICTURE

1. Hypertension: & oedema due to Na+& H2O may be ***severe & malignant*** usually is mild
2. Hypokalemia: see " kidney ". + renal escape phenomenon
3. Metabolic alkalosis: see " kidney ". → leads to tet
4. Polyuria. ↓ K+ made Kidney irresponsive to action of ADH
   Nephrogenic DI NS

INVESTIGATIONS

↓ K+ → Weakness, Constipation, Arrhythmia, NDI, Impaired gic tolerance? (↓ GIC K+ when ↓ K+)

1. Blood Chemistry:

- Increased: *Na,* *HCO3,* *Aldosterone.*
- Decreased: *K,* *Plasma rennin activity.*

2. Imaging: Urine ↓ Na, ↑ K+ + acidic urine + tetra-hydroaldosterone

- CT & MRI: *abdomen will differentiate between adrenal tumours & hyperplasia.*

3. ECG:

- Evidence of Hypokalemia: see " Kidney ".

TREATMENT

1. For adenoma: surgical removal. or irradiation
2. For hyperplasia: spironolactone 100 – 400 mg daily (K – sparing diuretic).
   Gynaecomastia
   Triametrine amiloride

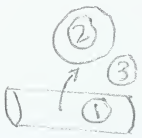
SECONDARY HYPERALDOSTERONISM

DEFINITION

- It is an increased activity of the RAAS.

ETIOLOGY

1. Renin overproduction:
   - Accelerated & Malignant hypertension.
   - Renal artery stenosis.
   - Bartter's hyperplasia of JGA
2. Hypovolemia:- with oedema
   - Heart failure.
   - Liver failure.
   - Nephrotic syndrome.
   - Excess diuretics.



3rd space loss =loss of fluid into interstitial space

CP; HTN & oedema severe
RAS 3rd space loss

INVESTIGATIONS

1. Increased: Plasma rennin activity Plasma aldosterone.
2. Serum Na: may be low in cases of Hypovolemia.

Echo, LFTs

TREATMENT

No surgical removal

1. ACE inhibitors.
2. Spironolactone.
3. TTT of the cause.

DISORDERS OF LIPID METABOLISM

HYPERCHOLESTEROLEMIA

1. **Primary:** Familial Hypercholesterolemia (FH).
2. **Secondary:**
   - Hypothyroidism.
   - DM.
   - Obstructive jaundice.
   - Nephrotic syndrome.
   - DRUGS: *Diuretics (Thiazides, Frusemide).*

HYPOCHOLESTEROLEMIA

1. Hyperthyroidism.
2. Malnutrition, Malabsorption.
3. Chronic infections: *AIDS, TB.*

HYPERTRIGLYCERIDEMIA

1. Metabolic: *DM, CRF.*
2. Obesity.
3. Alcoholism.
4. DRUGS: *Diuretics (Thiazides, Frusemide), Estrogen.*